# Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/Missouri-Medicine March/April 2016




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# Missouri Medicine

*The Journal of the Missouri State Medical Association - Since 1904*

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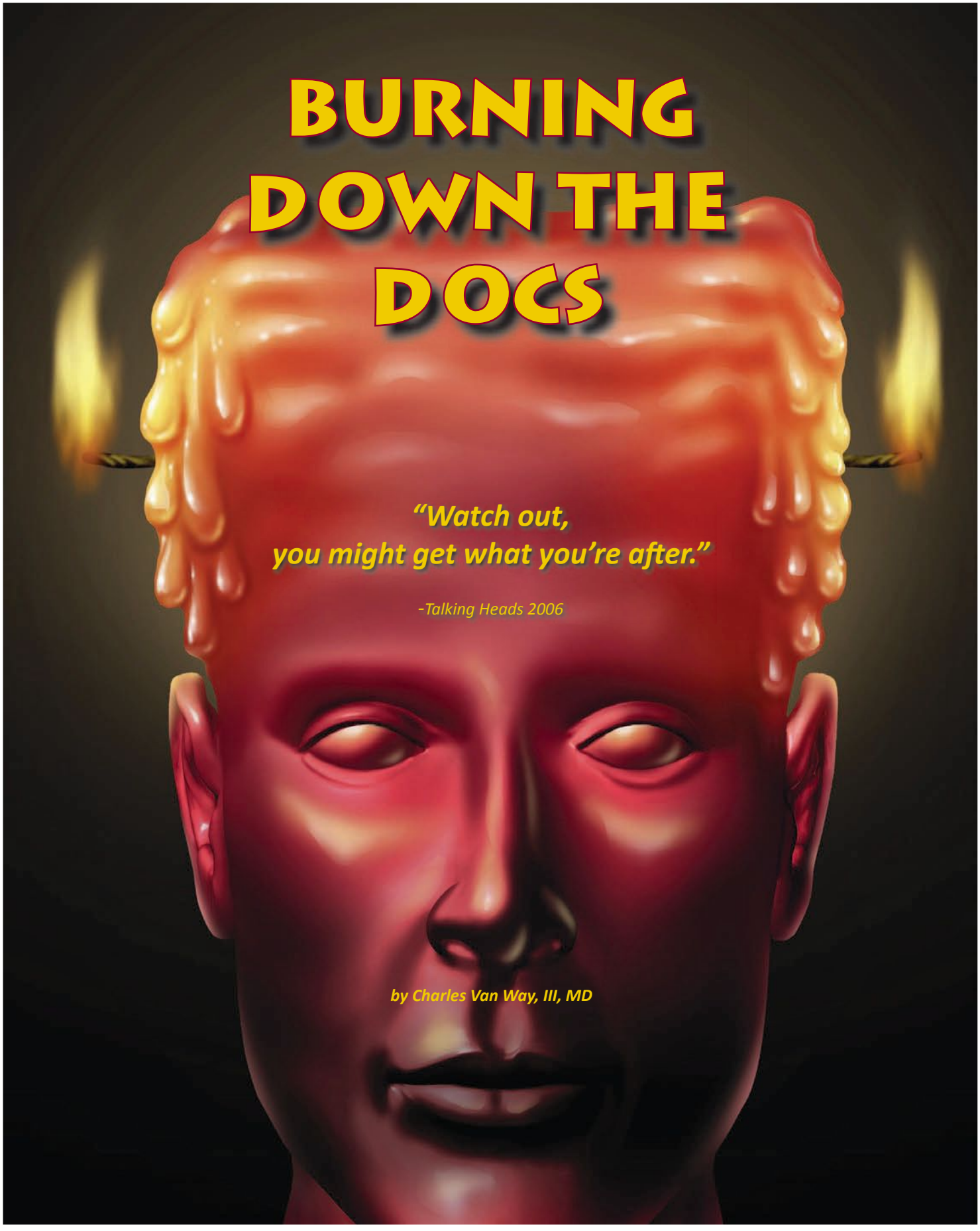
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BURNING DOWN THE DOCS
"Watch out,
you might get what you're after."
-Talking Heads 2006
by Charles Van Way, III, MD

Once again, let us take up the subject of burnout. There has been a great deal of talk over the last some years about this, including a piece by yours truly[2]. But it's not going away. It's getting worse. Some recent publications have focused on intensivists[3], the subject for today. In the most recent Medscape physician lifestyle survey, intensivists scored a 53% burnout rate[4]. This was the highest in the study. Emergency medicine physicians (the former champs!) scored 52%. Overall, physicians scored 46%. The level was 40% only two years ago. In the Medscape survey, burnout was defined as "loss of enthusiasm for work, feelings of cynicism, and low sense of personal accomplishment."[4] In more descriptive terms, you just don't give a flip anymore.

Burnout was found to be somewhat age dependent. The peak age range was 46 to 55. Burnout dropped off dramatically above 65. But the important message is this: burnout symptoms were seen in more than 40% of physicians from 35 to 65. That's most practicing physicians. Colleagues, if 40% of us just don't care anymore, we're in trouble.[4]

Back to intensivists? Besides the U.S. survey, an Australian survey noted very similar findings in 115 intensivists.[5] Some 80% had at least one symptom, with about 40% having all or most of the syndrome. Intensive care medicine shares some characteristics with emergency medicine. Both specialties require shift work, both have frequent (although predictable) night work, and both, apparently, are perceived to be associated with a loss of control over the working environment.

A study from France of critical care physicians and nurses showed a high rate in both. Some 50% of physicians and 33% of nurses showed symptoms. In physicians, burnout was associated with number of night shifts and time worked since last vacation. In nurses, it was associated with organizational factors and end-of-life issues. In both, it was associated with the occurrence of conflict situations. It's not very surprising that a happy workplace reduces burnout. That said, it is very doubtful that "happiness" appears on the list of objectives for critical care unit administrators. Evidently, it should.

We are moving strongly towards focusing critical care on intensivists, in the expectation that this will improve care. But if we destroy the physicians and nurses giving this care, we will not improve anything. Indeed, we may make things worse. And intensivists are only somewhat worse than physicians in general, 50% versus 40%.

What can we do? How can we make things better for our colleagues, and for ourselves?

There are outside or personal factors which can at least reduce the incidence of burnout. Physicians who do volunteer work were less likely to be burned out than those who do none. Almost any sort of volunteer work seemed to be associated with less burnout. Modest exercise (at least twice a week) was associated with less burnout. Physicians with "adequate" savings, self-reported, were less likely to have burnout symptoms. Attending church services was associated with less burnout. Interestingly, political affiliation (liberal versus conservative) had little effect[4]. So… marriage is good, volunteer work is good, church is good. Getting out of oneself seems to be a common factor. And financial security is also good. Hardly takes a survey to figure that one out. The advice "take time to take of yourself" remains sound.

But as good as these things may be, all are simply associations. They do little to get to the causes of the malaise. In the Medscape survey, participants were asked to report things they thought caused burnout. The top six were "too many bureaucratic tasks," too much time at work, too little income, increasing computerization (yes, electronic health records), the impact of the Affordable Care Act, and "feeling like just a cog on a wheel." This last captures much of the frustration felt by many physicians. It is somewhat disturbing that three or four of these six have been imposed on our profession by outside forces, be they hospital systems or government. Hence, they are outside our control, except as we can influence Congress, Federal bureaucrats, or hospital administrators. As the current saying goes, "Good luck with that."

Medicine has always been a stressful occupation, and will no doubt remain so. But stress and its effects seem to be getting worse. There are many forces converging to make physicians unhappy with their lot. Is it paranoid if some people are really out to "get" us? More to the point, as the health system is changing, many of the changes are adverse to physicians. These include the increased debt of young physicians, the loss of autonomy, the bureaucratic tasks, electronic medical records, and the ceaseless questioning of our judgement. And, of course, the ever-present risk of malpractice suits. Was this intended? Or is it simply a consequence of poor planning and implementation?

As sometimes said, "Never attribute to malice that which can be explained by stupidity." (While this is called Hanlon's Razor, sometimes Heinlein's Razor, similar thoughts go back at least to Goethe, and probably further back.[8] Even if no one was out to "get" physicians, many of the changes were made with little or no physician input, and without considering their effects on physicians.

Truly, we are getting the results to be expected from a badly-designed system. So, in the words of the song above, we have now "got what we're after." Neither medicine nor society at large is happy with this. And the term "designed" is definitely a misnomer. More accurately, we have something which simply evolved, and been tinkered with for the last century. We may choose to blame "Obamacare," but the Affordable Care Act introduced nothing new. It simply doubled down on many of the existing flaws of the system. But whether because of the ACA or because of prior factors, the pressure on physicians seems to be increasing. Many of us are frustrated, and burned out.

It shouldn't be this way. Besides taking care of ourselves as individuals, we need to take care of our profession as well. We need to become more radical, both as individuals and as groups. For example, one cause of stress has been the increasing number of physicians employed by large organizations. But that's also making it much easier for physicians to change jobs. Frustrated where you are? Get out. You may not have the autonomy of private practice, but you aren't tied down, either. After all, if you look for a new job, you will look at your present job in a new light. You may find you aren't so badly treated. Alternatively, you may actually find a better job. But either way, you force your employers to pay a lot more attention to keeping you happy, and productive, and on board.

But our organizations need to be stronger. The biggest criticism I hear about organized medicine is that its leaders "go along to get along." (Or is that the other way around?) We often support the status quo, when we should be disrupting it. Our organizations should express our grievances, loudly and often, and try to do something about them. And we should not be active just in our interests. Many patients are ill-served by our health care system. If we are to be their advocates, we must recognize their grievances. True, organizations must do a certain amount of political log-rolling. Compromise is the way political bodies work. But to compromise, we have to have to start from a firm position. Too often, our organizations just react, or else fiddle around the edges.



This is the best time to be advocates for ourselves, and for a better health system. Nobody likes Congress. Politicians are neither trusted nor respected. Physicians are more trusted than almost any other group in society. We had a physician, Ben Carson, seriously running for President (two, if you counted Rand Paul). OK, neither of them made it. But does anyone remember the last time that happened?[9] We have the credibility, the public respect, and the standing to clamor for changes.

It's time.

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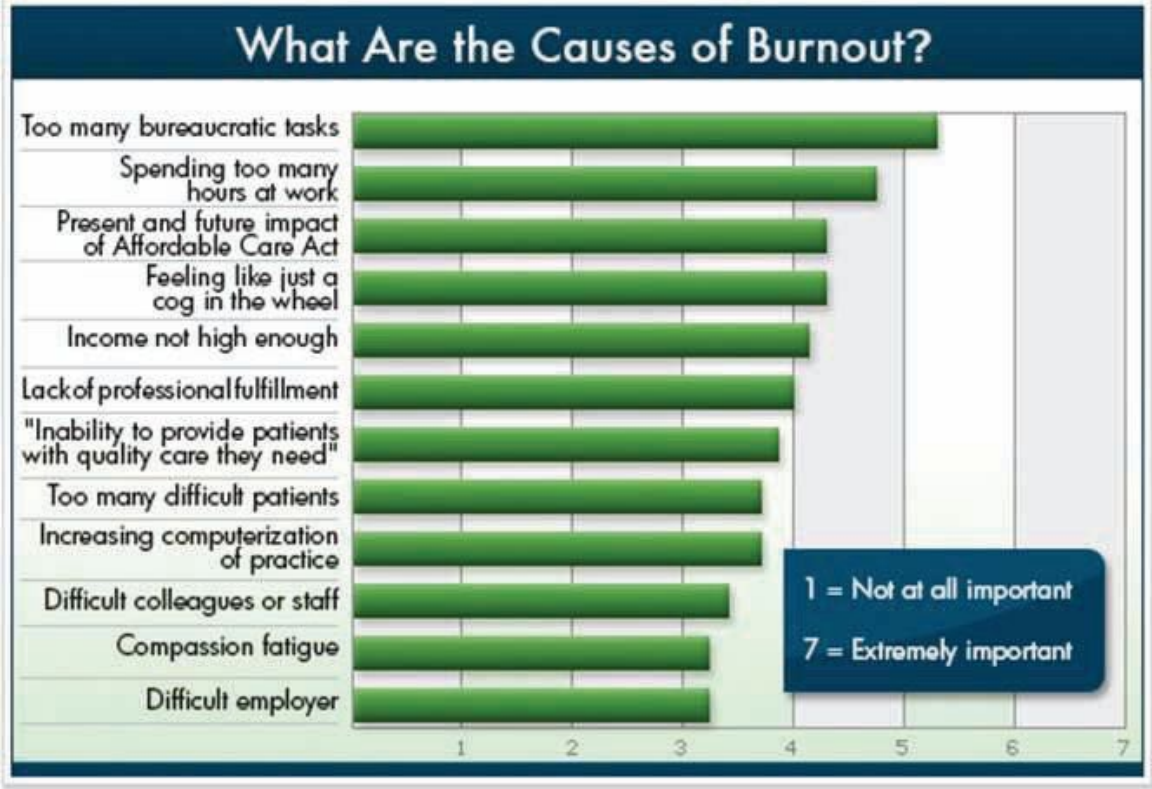


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# Problems with the 2015 Dietary Guidelines for Americans: An Alternative

*by James J. DiNicolantonio, PharmD, Zoë Harcombe, PhD & James H. O'Keefe, MD*

**The DGA have, once more, missed the opportunity to deliver a simple, memorable, effective dietary message to Americans: eat natural food and avoid processed food.**





James J. DiNicolantonio, PharmD, (left), and James H. O'Keefe, MD, (right), MSMA member since 2003, are at Saint Luke's Mid America Heart Institute, Kansas City, Missouri. Zoë Harcombe, PhD, is at the Institute of Clinical Exercise and Health Science, University of the West of Scotland.
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## Abstract

**The updated 2015 Dietary Guidelines for Americans, published in January 2016, have stirred much controversy since the advisory report first appeared. Several important changes have been made, with some recommendations having greater scientific evidence for their support than others. The focus of this review is to discuss specific recommendations from the 2015 Dietary Guidelines for Americans that lack sound scientific evidence; these include:**

**1) Allowing approximately half of all grains to be refined;**

**2) The continued recommendations for fat-free or low-fat dairy and limitation of saturated fat intake to <10% of calories;**

**3) Sodium intake < 2,300 mg/day; and**

**4) Consumption of up to 27 grams/day of "oils" (high in polyunsaturated fat or monounsaturated fat).**

**Based on our review, the aforementioned recommendations found in the updated 2015 Dietary Guidelines for Americans may increase the incidence of cardiometabolic disease, diabetes, obesity, dyslipidemia, cardiovascular disease, and possibly cancer.**

## Introduction

The Dietary Guidelines for Americans (DGA) is an extremely important nutritional document that influences the dietary habits of most Americans and can directly impact the health of the nation.[1] While lack of randomized controlled trials does not necessarily prohibit the prescribing of certain dietary recommendations, the overall evidence—from populations, observational studies, and clinical trials—must be taken into account to ascertain if each recommendation is scientifically sound. Thus, we reviewed the recommendations in the 2015 DGA and have noted several that not only lack sound scientific evidence but may have unintended consequences, such as promoting the very diseases they are trying to prevent.

Specific recommendations in the 2015 DGA that may increase the incidence of cardiometabolic disease, cardiovascular (CV) disease, and possibly cancer.

## "Grains, at Least Half of Which are Whole Grains"

The DGA report defines whole-grains as: whole-wheat bread; oatmeal; whole-grain cereals; popcorn; brown rice and whole-grain pasta. Refined grains are listed as: white bakery goods; bagels; pizza; grain-based desserts; refined cereals (corn flakes, rice cereals); tortillas; white rice and white pasta.[2] The 2010 DGA

acknowledged that usual whole-grain consumption in the United States (US) met only 15% of the target, while refined grain consumption was nearly twice the goal level.[3]

Grains are a relatively recent addition to the human diet, added approximately 10,000 years ago with the invention of agriculture. Their integration into the diet allowed human beings to move away from their traditional hunter-gatherer-type eating pattern. Cereal grains as consumed today, whether defined as whole or refined, would not be found in nature and thus humans did not evolve eating such substances. Common sense would advise caution being applied to recommendations to consume more of relatively recent adaptations to the food chain.

As the DGA documented consumption confirms, most grain intake is refined and most grain intake is part of a more broadly processed product, for example pizza, desserts, cookies, and muffins. Refined and whole-grain products tend to be high in added sugar and ingredients generally added during manufacture. Grain-based desserts are the single highest source of calories in American citizens aged two years and older.[3] In addition to the harm of added sugar, grains are nutritionally poor when compared with the essential fats, complete protein and micronutrients provided by meat, fish, eggs, vegetables, fruits, nuts and seeds—the diet for which humans are evolutionarily adapted.[4]

The recommendation to consume grains is ultimately a recommendation to increase the consumption of carbohydrate. Allowing almost half of all grains to be of the more refined type may particularly increase the incidence of cardiometabolic disease, diabetes, and obesity. Indeed, replacing fat with carbohydrate (in most instances refined grains) has been found to increase small-dense low density lipoprotein (LDL).[5-7] This results from an increase in triglyceride in very low LDL (VLDL), leading to triglyceride-rich LDL and the formation of small-dense LDL.[8] Small-dense LDL does not bind to the liver's LDL-receptors as well as native LDL and thus remains present in the blood longer, making these LDL particles more susceptible to oxidation. Moreover, small-dense LDL particles are inherently more susceptible to oxidation and penetrate into the sub-endothelium more readily than large buoyant LDL because they are smaller and denser.[9] Hence, small-dense LDL are undoubtedly more atherogenic than large buoyant LDL.[10] Thus, the consumption of grains, and in particular refined grains in the place of dietary fat may increase the amounts of small-dense LDL shifting the LDL pattern from the less atherogenic type (Pattern A) to one that is more atherogenic (Pattern B). Moreover, if grain replaces dietary fat, this may also lead to an increase in weight gain, fat mass, insulin resistance, a reduction in HDL, and an increase in triglycerides.[11-13] Thus, the recommendation to consume grains (whole as well as the more refined type) may increase the incidence of cardiometabolic disease and hence, CV disease.

### *Summary*

The recommendation to consume grains (particularly of the refined type) will likely lead to a decrease in HDL and an increase in triglycerides, small-dense LDL, insulin resistance, obesity, and hence increase the risk of the metabolic syndrome, diabetes, dyslipidemia, obesity, atherosclerosis, and CV disease.

### *An Alternative Recommendation*

Avoid grains and consume instead more natural, nutrient dense foods, such as meat, fish, eggs, vegetables, fruits, nuts, and seeds.

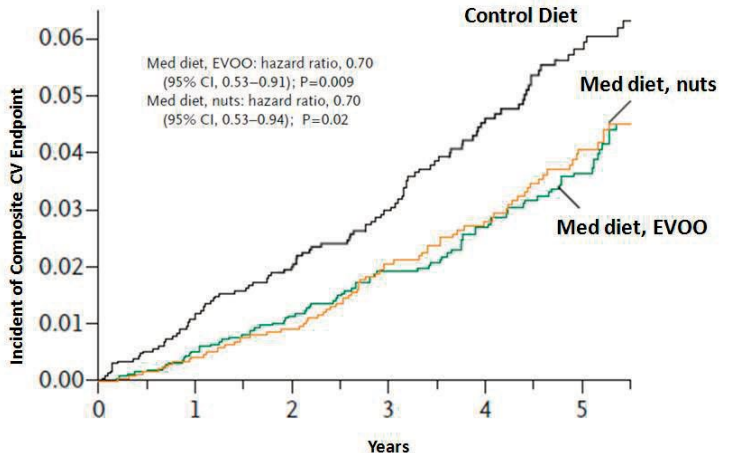
## "Choose Fat-free or Low-fat Dairy" and "Consume < 10% of Calories from Saturated Fat"

Numerous clinical trials in humans have either recommended consuming less animal/saturated fat (and hence an increased consumption of fat-free/low-fat dairy) or replacing animal/saturated fat (full-fat dairy for example) with polyunsaturated fat (mainly vegetable oils), which has not led to a reduction in CV disease.[13] More importantly, there is no evidence that consuming fat-free or low-fat dairy or reducing the intake of saturated fat in general from clinical trials in humans improves health outcomes.[14-16] Moreover, low-fat dairy formulations are generally higher in added sugars and thus this recommendation may lead to an increase in the consumption of added sugars and hence increase CV risk.[17]

Dietary fat not only provides satiety but also enhances absorption of fat-soluble vitamins.[14] The recommendation to consume fat-free or low-fat dairy may increase the risk of deficiencies of fat-soluble vitamins (A, D, E, and K). The low-fat advice beginning in the 1980s was associated with a steep increase in rates of diabetes and obesity in the U.S.[13] Hence, the continued advice to consume low-fat dairy and restrict saturated fat intake to < 10% of calories is repeating history but expecting a different outcome. The unintended consequences of eating low-fat dairy or restricting saturated fat intake includes an increase in the intake of refined carbohydrates and sugar (despite a recommendation to restrict the latter to < 10% of total calories). It is illogical to presume that low-fat versions of natural foods (which have had their inherent fat artificially removed) are healthier than their full-fat versions (as they are found in nature). Some populations with exceptional longevity, such as the Sardinians of Italy, do not consume fat-free or low-fat diary but full-fat

dairy. The French, have the highest intake of saturated fat in Europe and the lowest rate of CV disease.[18] Massai and Samburu warriors, who consume ample amounts of full-fat milk, have much lower rates of hypertension and CV disease compared to the Western world.[19,20] The Kitavans, who consume 17% of total energy as saturated fat (from coconuts) appear to have a virtual absence of ischemic heart disease and stroke.[21] The body needs to obtain dietary fat from somewhere, and if dairy fat (or saturated fat) is replaced with fat from vegetable oils, this may lead to an increased risk of CV events, CV death, premature mortality, and cancer.[13,22] Moreover, low-fat versions of natural foods such as dairy are less satiating and will likely result in an increased total caloric intake throughout the day, increasing the risk of obesity.[14]

***Figure 1***
***Kaplan-Meier Estimates of the Incidence of Outcome Events in the Total Study Population***
The incidence of the primary end-point (a composite of acute myocardial infarction, stroke, and death from CV causes). Hazard radios were stratified according to center (Cox model with robust variance estimators). CI denotes confidence interval, EVOO extra-virgin olive oil, and Med Mediterranean.




### *Summary*

Reducing the intake of full-fat dairy and saturated fat in general may lead to an increased intake of refined carbohydrate and sugar, and hence may increase the risk of diabetes, obesity, and CV disease. Moreover, reducing the intake of these natural animal fats may increase the risk for fat-soluble vitamin deficiency.

### *An Alternative Recommendation*

Eat natural foods, meat, fish, eggs, dairy products, avocados, nuts and seeds, and the natural fats contained therein.

## "Consume Less than 2,300 mg of Sodium per Day"

The Institute of Medicine (IOM) recently reviewed the literature regarding sodium intake relating to CV risk. They concluded that there was no evidence for reducing the intake of sodium to < 2300 mg/day.[23] Furthermore, the IOM noted that this recommendation may increase the risk of CV disease/premature mortality. Additionally, there is no evidence from clinical trials that reducing the intake of sodium per se reduces the risk of CV disease. A meta-analysis of prospective cohort studies and randomized clinical trials indicates that restricting sodium intake to less than 2.65 grams per day will likely increase the risk of CV events and all-cause mortality.[24] While reducing the intake of sodium may lower blood pressure, the increase in heart rate and adverse changes in counter-regulatory hormone levels more than offsets its supposed benefit.[25] When the increases in noradrenaline, adrenaline, renin, angiotensin-II, aldosterone, triglycerides, and cholesterol are taken into account, sodium restriction seems to cause an overall increased CV risk.[26] Numerous studies indicate that sodium restriction increases the risk of CV events and total mortality.[24,27,28] Sodium intake in animals, just like humans, is determined by need.[29] It is illogical to think that conscious sodium restriction is possible, or that it will lead to improved health outcomes. The sodium issue may have arisen from a lack of distinction being made between sodium and the sources of sodium in modern diets. The DGA documents sources of sodium in the American diet in great detail, from soups and condiments to burritos and ready meals.[3] Virtually no natural food is reported as a source of sodium. Processed food per se is generally unhealthy; sodium per se is not.

### *Summary*

Reducing the intake of sodium leads to the activation of the renin angiotensin aldosterone system as well as the sympathetic nervous system. These effects seem to outweigh any small reduction in blood pressure.

### *An Alternative Recommendation*

Eat natural foods, meat, fish, eggs, dairy products, nuts and seeds and the natural sodium contained therein.

## "Oils High in Polyunsaturated (Omega-6) Fat"

The DGA state, "The recommendation for oils in the Healthy US-Style Eating Pattern at the 2,000-calorie level is 27 g (about 5 teaspoons) per day."[1] "Commonly consumed

oils extracted from plants include canola, corn, olive, peanut, safflower, soybean, and sunflower oils." "The fat in some tropical plants, such as coconut oil, palm kernel oil, and palm oil, are not included in the oils category because they do not resemble other oils in their composition."

The strongest evidence from meta-analyses of randomized controlled trials suggests that the recommendation to replace saturated fat with omega-6 fat high in linoleic acid (mainly from industrial seed/vegetable oils) will increase the risk of cardiovascular events, cardiovascular death, all-cause mortality.[13,22,30] Additionally, the recommendation to consume up to 27 grams per day as vegetable oils may increase the risk of insulin resistance, diabetes, obesity, and cancer.[13,31] An increase in vegetable oils (and hence linoleic acid) will likely increase the susceptibility of LDL to oxidation and hence increase atherosclerotic plaque formation and cardiovascular events.[32]

Vegetable oils were never a part of the diet of early humans. Only in the past century have human beings consumed vegetable oils in any substantial quantity. The increase in the intake of vegetable oils has paralleled the rise in chronic disease in the U.S.[33,34] Moreover, we are unaware of any population that is relatively free of heart disease that consumes such high amounts of industrial seed/vegetable oils as recommended by the Dietary Guidelines.

Among the strongest randomized controlled trial evidence available comes from the PREDIMED Study,[35] which tested Mediterranean diets (MeDiets) supplemented with either olive oil or nuts, versus a control group assigned to a low-fat American Heart Association (AHA) Diet. The two MeDiets were quite high in total fat (about 40% of total calories) and in the 7,447-patients significantly lowered the primary endpoint (myocardial infarction, stroke, or death from CV causes) by 30% and 28% in the olive oil and nuts arms, respectively compared to the AHA Diet. (See Figure 1) These high-fat MeDiets also reduced the occurrence of new diabetes, atrial fibrillation, breast cancer, cognitive decline, blood pressure, and also slowed progression or induced regression of carotid artery intimal-medial thickness and carotid plaque.[36-41] Another MeDiet in a secondary prevention trial led to an approximate 70% reduction in cardiovascular events and all-cause mortality in the secondary prevention Lyon Diet Heart Study.[42] MeDiets do not encourage intake of industrial seed oils, which may be related their health benefits.. Table 1 summarizes our recommendations.

***Table 1***
***Summary of recommendations in the 2015 DGA that may increase the incidence of cardiometabolic disease, diabetes, obesity, dyslipidemia, CV disease and cancer.***

| RECOMMENDATION | REPLACE WITH | REASONING |
|---|---|---|
| "Grains, at least half of which are whole grains" | Avoid grains and consume instead more natural, nutrient dense foods, such as meat, fish, eggs, vegetables, nuts and seeds. | The recommendation to consume refined grains will likely lead to an increase in triglycerides, small-dense LDL, insulin resistance, fat mass and reduce HDL, hence increase the risk of the metabolic syndrome, diabetes, dyslipidemia, obesity, atherosclerosis, and CV events. |
| "Consume fat-free or low-fat dairy" and "< 10% of calories from saturated fat" | Eat natural foods, meat, fish, eggs, dairy products, nuts and seeds and the natural fats contained therein. | Reducing the intake of full-fat dairy and saturated fat may increase the intake of refined carbohydrates and sugar, hence may increase the risk of CV disease. Moreover, reducing the intake of these natural animal fats may increase the risk for fat-soluble vitamin deficiency and obesity. |
| "Consume less than 2,300 mg of sodium per day" | Eat natural foods, meat, fish, eggs, dairy products, nuts and seeds and the natural sodium contained therein | Restricting the intake of sodium to < 2,300 mg/day will likely increase the risk of CV events and all-cause mortality. |
| Oils high in polyunsaturated (omega-6) fat | Eat natural foods, meat, fish, eggs, dairy products, and seeds and the natural saturated and unsaturated fats contained therein. | The recommendation to replace saturated fat with industrial seeds oils will likely increase the risk of CV events, CV death, mortality, and cancer. |

### *Summary*

The recommendation to consume up to 27 grams per day of industrial seed/vegetable oils should instead be specifically recommending increased intake of olive oil and nuts, particularly in the context of a traditional MeDiet that is high in vegetables and fish, and low in processed foods, refined carbohydrates, and added sugars.

### *An Alternative Recommendation*

Eat natural foods, meat, fish, eggs, dairy products, and seeds and the natural saturated and unsaturated fats contained therein.

## Conclusion

Several recommendations in the 2015 DGA lack sound scientific evidence. The recommendations discussed in this review, such as the consumption of grains, low-fat dairy, saturated fat intake < 10% total calories, sodium < 2,300 mg/day, and industrial seed/vegetable oils up to 27 grams per day, may lead to unintended consequences such as an increased incidence of cardiometabolic disease, diabetes, obesity, dyslipidemia, CV disease, and cancer. The DGA

have, once more, missed the opportunity to deliver a simple, memorable, effective dietary message to Americans: eat natural food and avoid processed food.

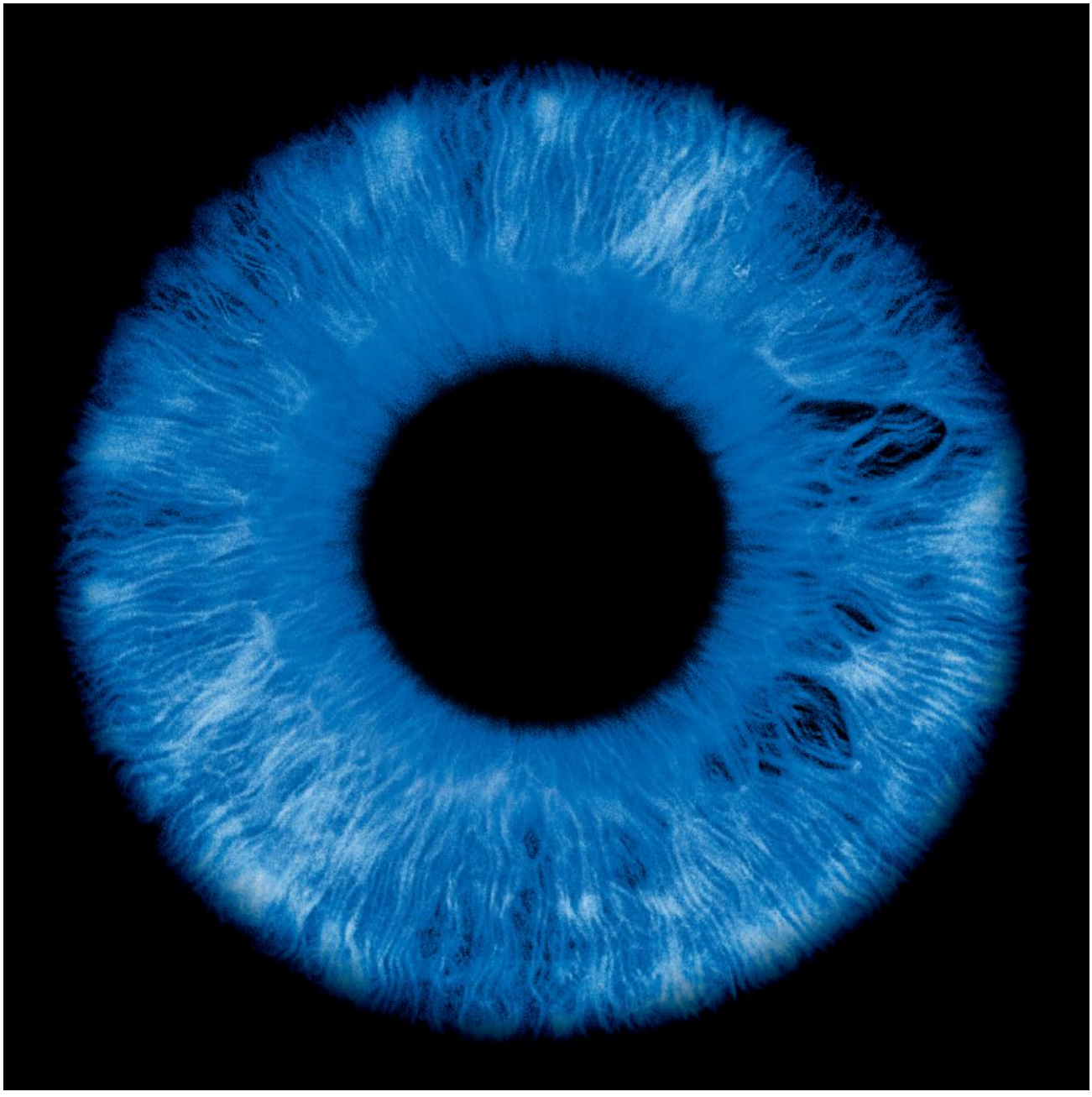
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## Disclosure

ZH receives income from writing about diet and nutrition. **MM**

# More than Meets the Eye: Eye Color and Alcoholism



*by Joel C. Eissenberg PhD*

**Studies found a statistically significant association between blue eye color and alcohol dependency among Americans of European ancestry. Here, I discuss the basis for light eye color and the evidence for a genetic contribution to risk for alcohol dependency.**

## Introduction

Upon first encountering a new patient, a good physician notes physical features that suggest increased risk of pathology. For example, an obese patient should probably be tested for diabetes. A patient with clubbed fingernails or toenails should be evaluated for pulmonary insufficiency. A patient with extensive tattoos may be a candidate for hepatitis testing.

Inferring behavioral pathology from casual inspection is much more challenging. However, a recent paper suggests that blue-eyed Americans of European ancestry are at higher risk for alcohol dependency than brown-eyed Americans. Is this finding a basis for special scrutiny of blue-eyed patients?

## Genetics of Eye Color

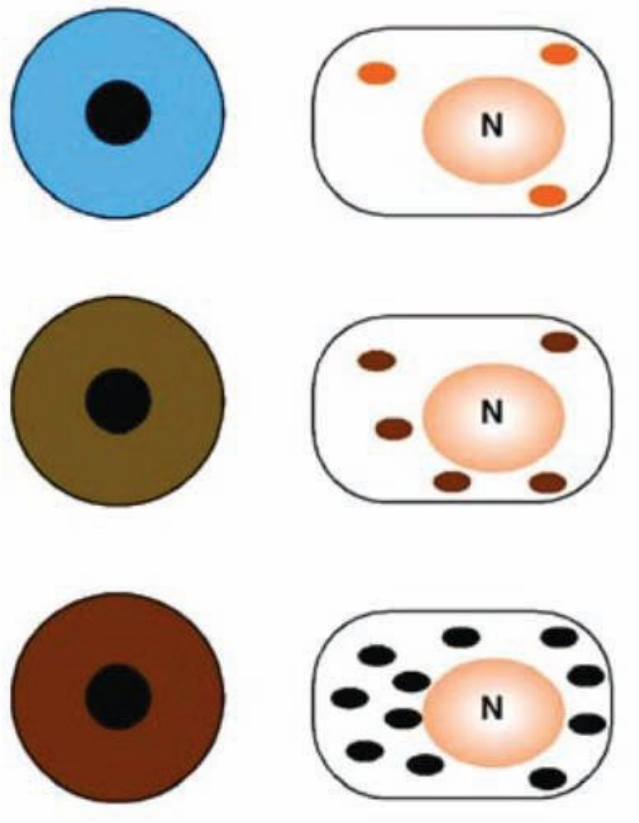
Eye color in humans is the result of variation in the number and size of melanin-containing organelles called melanosomes that are themselves contained in cells called melanocytes that are distributed within the outer iris stroma (See Figure 1). The number of melanocytes is similar among the different iridial colors. Blue eye color results from having few melanosomes, causing short wavelength visible light (the blue end of the spectrum) to be reflected. People with more melanosomes have hazel/green eyes; those with the most melanosomes in their iris stromal melanocytes reflect the least blue light and have brown eyes

Most Americans are taught that eye color is a single-gene trait - that a brown-eye gene variant is dominant over the blue-eye variant. The reality is somewhat more complex. The OCA2 gene on human chromosome 15 has a major impact on eye color by producing a protein that controls melanin formation and processing.[1] The more OCA2 activity in the iris melanocytes, the darker the eye color. However, as many as seven other genes can impact melanin deposition, resulting in shades of blue and green and explaining why two blue-eyed parents can have green-eyed children.

Eye colors other than brown only occur in individuals of European descent. The current genetic evidence suggests that the first humans had brown eyes. As our ancestors migrated out of Africa, some found their way into Europe. About 6,000-10,000 years ago, probably in the area of the Black Sea, a single individual was born with a mutation that programs reduced OCA2 gene expression and blue eyes.[1] The evidence suggests that all people with blue eyes carry this same variant. So the parts of the world where descendants of that founder individual are most common have the highest frequency of blue eyes; where those descendants are rare, darker eye colors are the dominant eye color.

***Figure 1***

Eye color is determined by the number and melanin content of melanosomes within the melanocytes of the anterior iris stroma. Left: representations of the pupil (black) and surrounding iris color in (top) blue eyes, (middle) hazel eyes and (bottom) brown eyes. Right: melanosomes (colored ovals) increase in number and melanin content in (top) blue eye melanocytes, (middle) hazel eye melanocytes and (bottom) brown melanocytes. N = melanocyte cell nucleus. Adapted from http://www.bioscience-explained.org/ENvol4_1/pdf/eyecoloureng.pdf.




## Genetics of Alcohol Dependency

The 4th edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric association classifies behavior as alcohol dependency if it meets three of the following seven criteria in a twelve month period:

- tolerance;
- withdrawal symptoms or clinically-defined alcohol withdrawal syndrome;

**Table I. Candidate genes for alcohol dependence (modified from ref. 6)**

| Pathway | Gene | Gene product function |
|---|---|---|
| GABA | *GABRA2*[21] | GABA receptor subunit |
| | *GABRG3*[16] | GABA receptor subunit |
| | *GABRA6*[22] | GABA receptor subunit |
| | *GABRB1*[22] | GABA receptor subunit |
| | *GABRB2*[23] | GABA receptor subunit |
| | *GABRB3*[24] | GABA receptor subunit |
| Muscarinic receptor | *CHRM2*[25] | muscarinic acetylcholine receptor |
| Taste receptors | *TAS2R16*[26] | gustducin-coupled receptor |
| Nicotinic receptors | *CHRNA5*[27] | neuronal nicotinic acetylcholine receptor |
| Opioid | *OPRK1*[28] | G-protein coupled κ opioid receptor |
| | *PDYN*[28] | ligands for κ-type opioid receptors |
| | *OPRM1*[29] | G-protein coupled μ opioid receptor |
| | *OPRD1*[30] | G-protein coupled δ opioid receptor |
| Alcohol metabolism | *ADH4*[17] | alcohol dehydrogenase |
| | *ADH1C*[31] | alcohol dehydrogenase |
| | *ADH5*[32,33] | alcohol dehydrogenase |
| | *ADH7*[33] | alcohol dehydrogenase |
| | *ALDH1A1*[33] | aldehyde dehydrogenase |
| | *ALDH2*[27,33] | aldehyde dehydrogenase |
| | *CYP2E1*[33,34] | cytochrome P450 |
| | *ADH1A*[17] | alcohol dehydrogenase |
| Other | *TACR3*[35] | G-protein coupled tachykinin receptor |
| | *ACN9*[36,37] | succinate dehydrogenase complex assembly factor |
| | *NPY*[29,33] | neuropeptide Y |
| | *NFKB1*[38] | NFκ-B transcription factor |
| | *AKAP9*[39] | protein phosphatase 1 regulatory subunit |
| Stomach/gastrointestine | *CCK*[33] | cholecystokinin |
| | *CCKAR*[33] | cholecystokinin A receptor |
| | *CCKBR*[33] | cholecystokinin B receptor |
| Dopamine | *DRD2*[36,37,40] | dopamine D2 receptor |
| | *DRD3*[41] | dopamine D2 receptor |
| Glutamate | *GAD1*[42,43] | glutamate decarboxylase |
| | *GRM8*[44] | G-protein coupled metabotropic glutamate receptor |
| | *GRIN1*[39,45] | N-methyl-D-aspartate receptor |
| | *GRIN2B*[32,39,45] | N-methyl-D-aspartate receptor |
| Serotonin | *HTR1A*[30,46] | G protein-coupled serotonin receptor |
| | *HTR1B*[25,47] | G protein-coupled serotonin receptor |
| | *HTR2A*[43] | G protein-coupled serotonin receptor |
| | *TPH1*[33] | tryptophan 5-monooxygenase |
| | *TPH2*[33] | tryptophan 5-monooxygenase |
| | *SLC6A4*[43] | serotonin transporter |

- use in larger amounts or for longer periods than intended;
- persistent desire or unsuccessful efforts to cut down on use;
- significant time spent obtaining alcohol or recovering from its effects;
- social, occupational and/or recreational pursuits are reduced or abandoned because of use;
- continued use despite knowledge of alcohol-related physical or psychological harm.

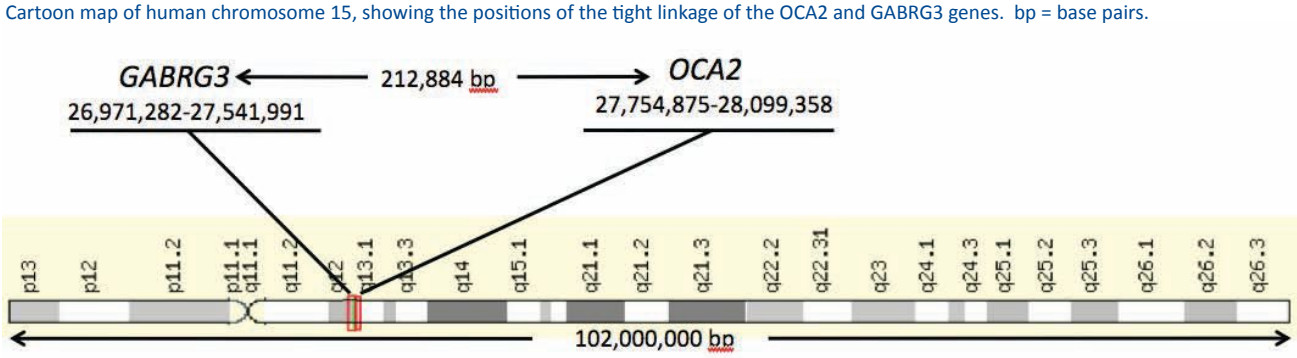
In 2013, alcohol dependency was formally reclassified together with alcohol abuse as "alcohol use disorder (AUD)."

Excessive alcohol use is the third leading modifiable cause of death in the United States.[2] In 2012, approximately 11.2 million adult men, 5.7 million adult women and 855,000 persons aged 12-17 had AUD in the U.S. (http://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-use-disorders). Excessive alcohol consumption kills about 88,000 people in the U.S. each year. A 2006 Centers of Disease Control study estimated the cost of excessive alcohol consumption to be $223.5 billion, reflecting a toll on workplace productivity, health care expense, criminal justice expenses and from motor vehicle crashes (http://www.cdc.gov/features/alcoholconsumption/).

Alcohol use disorder has an estimated heritability of 40-60%,[3-6] with complex underlying genetics. Genome-wide association studies and candidate gene analyses have identified many gene variants significantly associated with alcohol dependency. Many of these genes encode proteins important for neurotransmitter signaling, receptors activated by drugs and enzymes required for alcohol metabolism (See Table 1). The individual association of each of these genes with the risk of alcohol dependency is relatively weak. Rather, as with other complex traits such as BMI or cancer risk, risk is the result of the cumulative effect of multiple variants with modest individual impact.

It is important to appreciate that variants of genes that decrease alcohol dependency have also been described. For example, a variant of the ALDH2 gene is associated with low-dose alcohol-induced facial flushing reaction in persons of East Asian descent, leading to alcohol aversion and a lower frequency of alcoholism in this cohort.[7] Types and frequencies of alcohol tolerance and alcohol sensitivity variants differ in different populations, and are unlinked from the major eye color-determining variants.

***Figure 2***
Cartoon map of human chromosome 15, showing the positions of the tight linkage of the OCA2 and GABRG3 genes. bp = base pairs.




## Is Pale Eye Color Associated with Elevated Risk of Alcoholism?

A recently published study looked at over 1,200 people who were either diagnosed alcoholics or were similar in age, sex, and ethnic background (European descent) but were not alcoholics although they did occasionally consume alcohol.[8] What the study found was a higher statistical correlation between lighter eye color and alcoholism than between brown eye color and alcoholism, and the correlation was markedly higher for blue eyes.

This is not the first association to be made between eye color and alcohol use. A study of 10,860 Caucasian adult male inmates in the Georgia state prison system found that 42% of light-eyed inmates had alcohol abuse problems while the fraction of dark-eyed inmates with alcohol abuse problems was 38%.[9] The same report also examined data from 1,862 Caucasian American women, and found that light-eyed women reported significantly more alcohol than dark-eyed women. In both cases, the effect sizes were small, but the samples were not corrected for population stratification. The more recent study did statistical tests to demonstrate that the samples were moderately homogeneous. That said, the strength of the association they found was modest: the odds of a blue-eyed person being alcohol dependent is 1.8 fold higher than an American of European descent with brown eyes. This is comparable to the association between type II diabetes and hypertension, which was examined in the Nationwide Inpatient Sample (NIS) database (~7.8 million cases). The study found that the odds of having hypertension were 2.2 times higher among patients with type II diabetes versus patients without type II diabetes.[10] In contrast, the risk of non-cardia gastric cancer is six to eight times higher for people infected with *Helicobacter pylori* than for uninfected people,[11,12] and smokers are 25 times more likely to develop lung cancer than people who never smoked.[13]

Why might having blue eyes put one at higher risk for alcohol dependency than having brown eyes? One possible explanation is that a gene lying near the OCA2 gene on chromosome 15 carries a mutation that leads to increased alcohol tolerance, and thus a tendency to drink too much. Indeed, the authors noted a tight genetic linkage between the OCA2 gene and a nearby gene encoding a cluster of γ-amino butyric acid (GABA) receptor genes, including the GABRG3 gene (See Figure 2). GABA receptors have been implicated in alcohol tolerance and alcohol dependency,[14,15] and surveys for genes associated with alcoholism identified GABRG3.[16,17] GABA is a major inhibitory neurotransmitter, so a mutation in a brain GABA receptor that reduced its ability to respond to GABA might impair an inhibitory response to alcohol. This would explain why people with such a mutation might continue drinking when others stop. One hypothesis is that the OCA2 blue-eye mutation resulting in blue eyes occurred on a chromosome that already carried a GABRG3 mutation. Since the OCA2 and GABRG3 genes are separated by only about 0.2% of the length of chromosome 15, the chromosomal coupling of a blue-eyed variant of OCA2 and an alcohol tolerant GABRG3 variant has been maintained in most descendents of the first blue-eyed human.

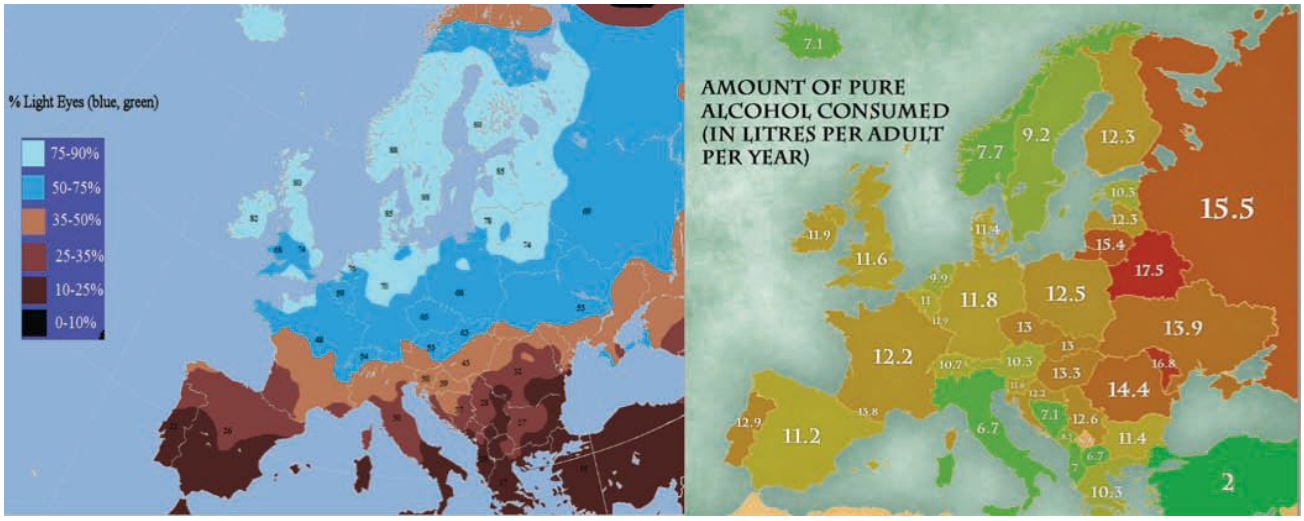
## Genetics, Risk, and Destiny

It is common to refer to "the gene for sickle cell disease" or "the gene for muscular dystrophy." In reality, there are no genes for diseases. The "gene for sickle cell disease" is actually the adult beta hemoglobin gene, which we all have. Sickle cell disease patients inherited a particular form, or "allele" of the beta hemoglobin gene that causes their red blood cells to sickle under low oxygen tension.

Similarly, there is no "gene for blue eye color" or "gene for alcoholism." The OCA2 gene plays a major role in eye color, and a genetic variant that reduces OCA2 gene expression accounts for most cases of blue eye color. The

***Figure 3***

Distribution of blue eye color does not explain per capita annual alcohol consumption across Europe. Left: percent light eye color across Europe (modified from: http://1.bp.blogspot.com/-eqhQhrOT-Ck/UAAA-9E-B0I/AAAAAAAAABc/o-4yE8Ou6i4/s1600/europe-eyes-general--lig.png). Right: per capita annual alcohol consumption by nation across Europe (modified from: http://jakubmarian.com/wp-content/uploads/2015/05/alcohol.jpg).




GABA receptor gene family encodes a family of proteins required for nerve cell function. There may be variants of one or more GABA receptor genes that make their carriers less sensitive to alcohol and thus raise risk for excessive alcohol consumption leading to dependency. Of course, there are also variants of genes implicated in alcohol sensitivity that result in increased alcohol sensitivity or intolerance. These could balance the effects of the blue-eye-color-associated alcohol tolerance variants. So in any given blue-eyed person, the statistical tendency towards alcohol dependency observed in the blue-eyed population may be amplified or offset by combinations of variants at other genes.

It is also important to appreciate that culture plays a large role in patterns of alcohol use. In the extreme case, most observant Muslims, Seventh Day Adventists and Southern Baptists abstain for religious reasons. In many cultures that do condone alcohol consumption, it is considered as a food, and alcohol abuse is subject to disapprobation. Regional cultural variations probably help explain why the rather uniform North-South cline in eye color across Europe is not mirrored by a similar cline in per capita annual alcohol consumption patterns (See Figure 3). Seasonal Affective Disorder (SAD) is a form of depression associated with a change in seasons—usually with the shorter daylight of winter—that is comorbid with alcohol dependency.[18] However, there appears to be no significant difference in the prevalence of SAD in Italy and Norway,[19] suggesting that latitude alone should not contribute significantly to alcohol dependency in areas where light eye color is most common. Further complicating things, light eye color appears to be protective for SAD.[20]

The author of this article has blue eyes and pale skin. Throughout adult life, he has been careful to wear long pants, long-sleeve shirts and a hat whenever practical, and to use sunscreen to avoid skin cancer. To have pale skin is not to have the gene for basal cell carcinoma or melanoma. But a person with pale skin is at higher risk for skin cancer and should be more vigilant to mitigate that risk through responsible behavior. Similarly, having blue eyes may mean that a person should be more vigilant about alcohol consumption to avoid the risk of becoming alcohol dependant.

Any routine patient history should include questions about alcohol consumption. There is also an online self-assessment tool to evaluate personal alcohol intake levels: http://www.alcoholscreening.org/Screening/Page04.aspx. Excessive alcohol consumption is a risk factor for heart disease, liver cirrhosis, and cancer. The evidence that blue-eyed Americans may be more susceptible to alcohol dependency shouldn't change that standard practice. Should evidence for alcohol dependency emerge through the history, counseling or other intervention may be appropriate, but eye color alone is not a sufficient guide to action.

Identifying and treating alcohol dependency is a worthy clinical and public health challenge. Alcoholics can be secretive about their addiction and frequently deny it long after it takes a toll on their families, friends and employers. While eye color per se is not a strong predictor of risk for alcohol dependency, the advent of personalized

medicine and the thousand dollar genome will soon allow comprehensively assessing patients for all known genetic risk factors, and counseling them accordingly.

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## Disclosure

None reported.




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# Is Health Care Reform a Gathering Storm for Doctors?

*by John B. Holds, MD*

**Medicare and Medicaid Act of 1965, Section 1801:**
**"Nothing in this act shall be construed to authorize any federal officer or employee to exercise any supervision or control over the practice of medicine or the manner in which medical services are provided…"**

The excerpt above from the original Medicare and Medicaid Act legislation of 1965 crystallizes the ethos of a bygone age, and seems inconceivably anachronistic as a line from modern Federal legislation. It is interesting how in the 20th century medicine went from a profession riddled with quackery, inadequate standards and training to a revered profession that absorbed some of the best and most capable minds in our society, devising and using an explosion of technological advances that changed the world. Physicians of my vintage (1983 medical school graduate) entered a world that expected precision, skill and 8-10 years of complete personal and financial sacrifice and commitment after college, but promised respect, autonomy, and generous financial rewards later. Historically, up to 90% of physicians from the 1960s through the 1980s would recommend medicine to their children as a career. Doctors loved their work, with most working long hours and retiring late in life.

Perceived as the cause of runaway fees and costs for medical care, the Center for Medicare and Medicaid services (CMS) pursued the diagnosis related group (DRG) system for hospital reimbursement, and ultimately placed a limiting fee on cataract procedures, as the first physician fee limitation CMS sought. This became comprehensive with the Hsiao study and implementation of the Relative Value Scale (RVS) in 1992. Deeply flawed, the RVS boxed physicians into a zero sum game for fees and services, which via the oxymoronically named Sustainable Growth Rate (SGR) of the years from the 1997-2015 eroded physicians' incomes on a year-to-year basis.

Commercial insurance has largely followed Medicare's lead in these matters, with RVS-based reimbursement, using the power of contracting with a large percentage of the population to push physicians into "contracts of adhesion" that doctors generally have no ability to negotiate, and must simply sign or be out of network, limiting many patients' access.

"This past fall I had the honor of presenting the Foundation lecture to my professional subspecialty society at the 46th annual meeting of the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS). I examined health care reform, challenges it creates for our specialty, the concerns of the ASOPRS members, and how they expect to respond to these concerns. Our branch of surgery has been under a CMS microscope for the past two years with pre- and post-payment reviews for functionally indicated upper eyelid surgery (blepharoplasty, ptosis repair and browlift). We have been subjected to unrelenting RAC and SMRC audits with updated, irrational and sometimes impossible to comply with Local Carrier Determination (LCD) policies. In my practice, apparently unending audits request an average of 5-15 charts per month for pre-or post-payment review (office + operating room). I respond with meticulous documentation and narrative explaining exactly how the documentation fully complies with the carrier's LCD policy. I now stand at over 200 charts they have requested, with no payments lost by my practice, but the physician (me) is very aggravated and tired of this travesty. Clearly this process is not about preventing and reclaiming payments from fraud and abuse, but is simply about abusing the providers of medically necessary and approved services.

I performed an email survey in June 2015 regarding issues challenging the practices of ASOPRS members. The

greatest threats related by members (in descending order) were decreasing payment for medically-necessary care, ACA and Federal-related regulatory expansion, time and aggravation of EHR compliance, increasing overhead, commercial insurance issues and decreasing income. "Mastering the growing body of oculofacial knowledge" was related as the next to lowest of 12 areas of potential concern, with the previously mentioned top areas of concern cumulatively being 23 times more important than maintenance of surgical competency to ASOPRS members. The revelation was that my colleagues are 23 times more concerned by a variety of largely Federal and commercial insurance-related issues than they are about maintaining technical competence. This survey also made me question why many of us were spending up to six days at our fall professional meetings. It would seem more rational for us all to spend a week in Washington lobbying our legislators.

Physicians have not proven to be the most effective at uniting and representing their interests on a national stage. The American health care system appeared to be broken at the time of enactment of the Affordable Care Act in 2009. Whereas the AMA rushed to endorse a concept, and gained nothing material for the practicing physician in the ACA, the pharmaceutical industry, insurance companies and hospitals were all big winners, harvesting benefits worth many billions of dollars to their industries. These interests maintained an intensive lobbying presence, obtaining administration and congressional guarantees of their priorities before supporting the bill. America's middle class and physicians were big losers."

The electronic health record (EHR) requirement of the ACA is a case in point. The federal incentives to adopt EHR don't even come close to covering the true costs. Add to that the disruption of practice, patient contact and work flow, along with the approximately one hour EHR adds to every physician's work day, and we have a mandate that has destroyed the remaining joy of practice for thousands of physicians (and was a final straw in many retiring). If the federal government wants doctors to complete EHR, they should pay us for the hour each day it takes. I don't think a trade union would allow an hour to be added to every workday without compensation. Electronic medical records may eventually reap benefits in cost and patient care, although thus far these advantages have been illusory at best.

Other rules and areas of compliance, such as maintenance of certification (MOC) for board certification, as well as a litany of new rules and regulations drain unproductive time and add cost and expenses to patient care, often unreimbursed. This compliance and certification may be desirable from a patient protection perspective, but medicine has reached a point where additional layers cannot be added without relief elsewhere.

"Although we may still do well financially in our practices, the increasing drains including compliance eating into free time, loss of productivity, insults-hassles-irritations, loss of status, and declining income leaves most US physicians in a position where they see medicine as a career in decline (84%). Fifty-eight to ninety percent of physicians would not recommend medicine as a career to their children. As those of us with mature practices, savings, and a concierge, cash practice or funded retirement to retreat to prepare to feather our nests, it makes one wonder, who will be taking care of the patients?

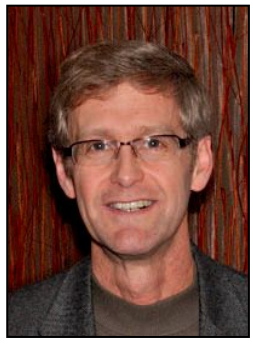
Being doctors we all try every moment to "do the right thing." For our patients and colleagues this often means selflessly providing care irrespective of family and personal demands or the patient's ability to pay. We have acquired our skills with eight to ten years of additional education and training after college, and most physicians enter practice with significant debt. A palette of declining benefits and increasing liabilities in the practice of medicine are not an encouraging trend and must be reversed to keep medicine viable. It is incumbent on every physician to work in concert to save our profession. We must become advocates for ourselves and through our professional organizations, with tangible defined goals and a collective will to persevere and see these goals enacted."

## References

-ASOPRS and Oculofacial Surgery - Current Challenges and the Future. ASOPRS Foundation Michael J. Hawes lecture, John B. Holds, MD, 46th annual fall scientific symposium, November 12, 2015, Las Vegas, NV.
-"Why doctors are sick or their profession." Sandeep Jauhar, Wall Street Journal, August 29, 2014
-http://www.physiciansfoundation.org/uploads/default/Physicians_Foundation_2012_Biennial_Survey.pdf

## Acknowledgment

This editorial is modified from this editorial published in January: Holds JB Audits overly burdensome to physicians. Ocular Surgery News, US edition, January 10, 2016. http://www.healio.com/ophthalmology/regulatory-legislative/news/print/ocular-surgery-news/%7B89129dba-d420-4243-ac07-1704bb36cce0%7D/audits-overly-burdensome-to-physicians



John B. Holds, MD, FACS, MSMA member sine 1991, is a Clinical Professor of Ophthalmology and Otolaryngology/Head and Neck Surgery at Saint Louis University, a former president of the Missouri Society of Eye Physicians and Surgeons, and a current legislative chair for that organization.
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# BEWARE

## Tax-Related Identity Thefts Return

Once again, the annual tax season has ushered in a rash of identity thefts among physicians.

For the third year running, physicians across the nation have filed their tax returns only to be told by the IRS that someone else already filed their return and made off with tax refund money.

In a recent twist, a victim was issued a credit card he had not requested, and the Post Office called to ask if he really wanted his mail forwarded to another address (he did not). This appears to be the work of an organized scam aimed particularly at physicians and dentists.

The U.S. Secret Service, the IRS, and the FBI have been investigating the matter, but the number of victims continues to pile up. More than 200 MSMA physicians have reported being hit.

The January/February edition of *Missouri Medicine* offered helpful hints on how to protect yourself from and what to do if you have become a victim.

Additional information can be found on MSMA's website at www.msma.org/tax-identity-theft-scams.

### Take these steps as soon as possible:

1. Call the IRS at (800) 908-4490, and report your suspected identity theft.
2. Call the Social Security Administration at (800) 772-1213, and let them know.
3. Place a fraud alert on your credit file by contacting one of the three credit reporting companies. The company you contact is required to contact the other two, which will then place a full alert on your credit report. The three companies are:
   - Equifax - (800) 525-6285 – http://www.equifax.com/home/en_us
   - Trans Union - (800) 680-7289 – http://www.transunion.com/
   - Experian - (888) 397-3742 – http://www.experian.com/
4. Fill out and submit the IRS Form14039, which can be found at this site: http://www.irs.gov/pub/irs-pdf/f14039.pdf
5. Please e-mail MSMA Executive Vice President Tom Holloway at tholloway@msma.org and provide your full name, home address, and telephone number. MSMA is working with the U.S. Secret Service and has been asked to provide the names of suspected victims.

### Consider visiting these websites for more information and tools to help you:

- Federal Trade Commission
  http://www.consumer.ftc.gov/articles/0008-tax-related-identity-theft

- Internal Revenue Service
  http://www.irs.gov/Individuals/Identity-Protection

- Social Security Administration
  http://www.socialsecurity.gov/pubs/EN-05-10064.pdf

**MM**

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## Don't Let All Your Days Be "Weak" Days: Make Someday Happen!

I read with much interest and pleasure your reprised editorial on Making "Someday" Happen (January/February 2016).

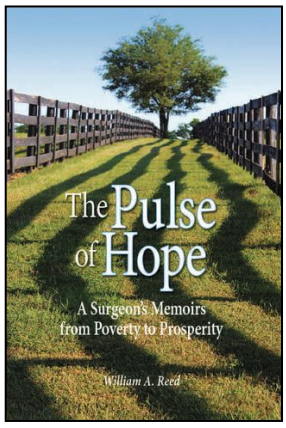
My wife and I, too, have always acted on the premise that we should not wait for "someday" to experience life and see wonderful new places. Doing them while we are functional physically and can enjoy them most seems common sense to us. We are fortunate to have been able to travel to many places and see many things during our years together, both in the U.S. and abroad.

What first caught my eye in your article were the action pictures from Queenstown, New Zealand,which brought back memories of a trip my wife Anne and I took there in January 2013. We had gone on a land/sea vacation involving a stay in Cairns, Australia, including a helicopter ride to the Great Barrier Reef which we snorkeled, followed by a stay in Sydney with a climb of the bay bridge, traveling to the Blue Mountains and seeing the Sydney Opera House, among other things. We then boarded a cruise ship, with a quick stop in Melbourne the next day, and then crossed the Tasman Sea to New Zealand for stops in multiple ports before finishing in Auckland a week later. The rest of our travel party flew home from there, but Anne and I decided to extend our trip for three days to visit Queenstown, the "adrenalin capital of the world" on New Zealand's south island, as suggested by a New Zealander friend that advised us not to miss Queenstown if we were making that long trip anyway. It turned out to be the highlight of our entire trip! While we didn't sky dive, we did parachute jump off the mountain, rode the Shotover River jet boats, the Luge, took Segway rides all over the town and visited the Kawarau Bridge bungee jump venue. Anne tried to talk me into a jump with her, but I demurred due to having had open heart surgery three months before and fearing that my sternum might not tolerate the G-forces. We still talk about the beautiful mountain range called "The Remarkables," the picturesque glacier lake, the wonderful B&B where we stayed, and all the fun we had there. Bottom line is that we, too, decided years ago to not wait for "someday" to experience as many of the things on our bucket list as possible and will continue to do whatever we can while we have good health and function.

I leave you with a story of a tee shirt I saw on a trip to Mackinac Island a few years ago – on the front was written: "Monday, Tuesday, Wednesday, Thursday, Friday, Saturday, Sunday. See, there is no Someday!"

Thanks for bringing back some precious memories!

*Tavo Chirino, MD*
*MSMA member since 1980*
*OB/GYN, St. Louis*




## The Pulse of Hope

**A Surgeon's Memoirs from Poverty to Prosperity**

***by William A. Reed***

***Reviewed by Lee A. Norman, MD***

BOOK REVIEW

This book is as subtle and understated as Bill Reed himself. But there are lessons in it that come through loud and clear, three of which particularly spoke to me. The first is about "taking credit" for the good things and the bad things that happen in one's life. Bill is the first person to stand up and be accountable when something doesn't go right, and he's the last person to accept accolades for those things that have gone not only well, but dramatically well. It is the mark of quiet heroism to credit others, and Bill has demonstrated that throughout his life.

The second lesson in the book is about efficiency – being economical with words (hint: Bill uses as few as necessary to quietly make his point) and about movement: his deft surgical skills have no wasted motion. If he were inclined to a career in music, he would have been a symphony conductor, one with very little dramatic and wasted flailing of the arms.

And finally, he demonstrates reverence of the sacred bond that exists between physician and patient, and doctor and colleague. This serves as the basis of trust we all have in this wise and quiet colleague.

Hardcover: 237 pages
Publisher: William Reed
ISBN-10: 0990740404
ISBN-13: 978-0990740407

# MSMA Members in the News

Read more about what our members are doing at www.facebook.com/momedical

*Missouri Medicine* announces a new member of our Editorial Board. Board members are selected on the basis of exceptional professional accomplishment and expertise in their specialty.



Michael L. O'Dell, MSHA, MD, FAAFP, MSMA member since 2010, is the new Family Practice member replacing Harold A. Williamson, MD, who served on the board since 2007. Dr. O'Dell is Associate Chief Medical Officer at Truman Medical Center and Professor and Chair of the Department of Community and Family Medicine at the University of Missouri - Kansas City.

Congratulations to these MSMA members, at Ellis Fischel Cancer Center in Columbia, who have recently been certified by MD Anderson Cancer Network: Drs. Kara Braudis, Kristen Fernandez, Nicholas Golda, Jonathan Harrison, Jeffrey Jorgensen, C. Daniel Kingsley, Debra Koivunen, N. Scott Litofsky, Gregory Renner, Steven Westgate, and Robert Zitsch, III. They have been members of MSMA for a total of more than 150 years!



An MSMA member since 2007, Brett Crist, MD, of Columbia, is making cutting-edge achievements with a new surgical technique that improves biological hip joint replacement.



Congratulations to William Dailey, MD, on celebrating the one-year anniversary of his practice in Osceola. MSMA appreciates his member support since 2010.



Phillip Foreman, MD (right), and Erik Meidl, MD, were honored with the Caring Heart Award by the Hannibal Free Clinic. Together, they have been members of MSMA for a total of 60 years.

Donald Kuenzi, MD received the Missouri University Medical School Distinguished Service Award for 2016. Dr. Kuenzi has previously received the Lifetime Achievement Award of the Kansas City Medical Society. He is the founder of The Gashland Clinic in Kansas City North.



Raghav Govindarajan, MD, has taken on numerous leadership roles in MSMA and within his specialty since becoming a member in 2013. The work he does with students at UMC is another example of his outstanding service to medicine. He has been honored with the National Golden Apple Award for Teaching Excellence from the American Medical Student Association.



An MSMA member since 1999, Bhagirath Katbamna, MD, has been unanimously elected as the new Board President of the Northeast Missouri Ambulatory Surgery Center, LLC, and Hannibal Anesthesia Associates, LLC.

MSMA would like to take a moment and recognize Carlyn Kline, MD, of St. Joseph, for the compassionate care she has provided to patients and also to peers, when faced with difficult circumstances. MSMA is extremely fortunate to have her membership support since 1976.



Alan Mead, MD (left), has been named Physician of the Year at Lake Regional Health System. He has been a member since 2001. Presenting the award is Patrick O'Neil, DO, MSMA member since 2014.



James O'Keefe, MD, has been a member of MSMA since 2003. His editorial contributions to readers of Lee's Summit Tribune are greatly appreciated, as is everything he does for heart health.



An MSMA member since 1987, Pat Smith, MD (left), of Columbia, has earned the honor of being inducted into the Missouri Sports Hall of Fame.



Congratulations to Michael Tentori, DO, for joining the Canton/LaGrange Family Practice. MSMA is grateful for his support since 2009.

**MM**

# St. Louis Metropolitan Medical Society - Building Relevance for Physicians

## History

The origin of the St. Louis Metropolitan Medical Society (SLMMS) dates back to 1836, when a group of concerned physicians gathered to share information about medical cases, public health concerns, and the need for an "organized group." This year SLMMS celebrates 180 years of operation, with a history that pre-dates both Missouri State Medical Association and the American Medical Association, and is proud to be one of the oldest continuing medical societies in the United States.

In 2013, to continue to chart its course and serve its members with relevance, SLMMS completed a strategic planning process that identified six key areas of focus -advocacy, communications and marketing, education, fiscal responsibility, leadership development and membership enhancement – with tactics necessary for success. SLMMS continues to operationalize this plan today. The world in which our physician members practice is continuously changing. This strategic roadmap helps guarantee that SLMMS will be there to provide support.

Through the process, SLMMS defined a new mission statement, "to support and inspire member physicians to achieve quality medicine through advocacy, communication and education." The Society also adopted its first-ever vision statement: "Physicians leading health care and building strong physician-patient relationships."



2016 SLMMS President
Sameer Cabbabe, MD



2015 SLMMS President
Michael Stadnyk, MD

SLMMS leaders are key stakeholders in delivering the mission, vision, and strategic plan. Michael J. Stadnyk, MD, 2015 SLMMS president, reminded members of the saying, "Think globally, act locally," during his recently-concluded year of service. "There are many issues influencing the world in which we live," explained Dr. Stadnyk, "and many are much larger than what any local medical society can change. So where can a St. Louis physician make an impact? Right here at home, in your own hospital, in your own office, and in your St. Louis Metropolitan Medical Society."

"SLMMS is the collective voice for physicians in both regulatory and legislative issues. We provide educational benefits, explore community service opportunities, and keep our members informed of timely issues," he added.

## Physician Leadership Institute

During Dr. Stadnyk's term as president, SLMMS launched its Physician Leadership Institute, developed in partnership with Anders Health Care Services and Healthcare Management Alternatives, Inc. The five-session program is open to physicians only, and focuses on the business side of medical practice, with the objective of helping physicians develop their leadership and management skills. The 2015 class filled to capacity, with 25 physicians from St. Louis and throughout Missouri completing the program.

The curriculum is rooted in the six domains of the Medical Group Management Association, and was developed with input from the SLMMS CME committee, health care executives, and the partnering consultants. The classes were designed to be interactive and encourage discussion, providing the participants with the presentations and reading materials in advance of the sessions, so that class time is optimized for debate and the exchange of information. The faculty includes experts from the St. Louis area on topics relevant to all practitioners, whether they are independent, hospital-based, or part of a large group.

The six domains are foundations of health care, finance and revenue, practice management, risk and compliance, and leadership skills. SLMMS feels the program is not only

filling a need in the physician community, but fulfilling a goal of its strategic plan by developing current and future SLMMS leaders.

## Issues Advocacy

SLMMS projects an active voice on key issues impacting the practice of medicine. When UnitedHealthcare began eliminating physicians from its Medicare Advantage physician network, SLMMS spoke out through the news media and grassroots communications, resulting in some doctors being reinstated. More recently, SLMMS has unified opposition to maintenance of certification rules, through proposed MSMA resolutions, educational programs, and in *St. Louis Metropolitan Medicine*, its bi-monthly journal.

## Resident-Fellow and Medical Student Sections

SLMMS has focused on building relationships within the two medical education programs in St. Louis. Over the last 18 to 24 months, SLMMS has formed Resident-Fellow and Medical Student member sections. Resident-Fellows pay significantly reduced annual dues and enjoy full membership benefits; medical student dues are free, and SLMMS amended its bylaws to give students voting representation on its Council, through appointed liaisons from both Saint Louis University and Washington University Schools of Medicine.



SLMMS student members from WUSM volunteering at World Food Day.

"By reaching out to younger members while they are still in training we are able to introduce them to organized medicine and the value of medical society membership," explained Samer Cabbabe, MD, 2016 SLMMS president. "In addition to involvement with our Council, we include these members in most Society events, providing them with beneficial networking and mentoring opportunities."

Connecting with the students has also provided SLMMS the opportunity to actively support many of their initiatives, such as the IDEA Labs entrepreneurship incubator at Washington University, and the newer MedLaunch program at Saint Louis University. Both organizations have received grant support from the St. Louis Society for Medical and Scientific Education (SLSMSE), the charitable foundation arm of SLMMS. SLSMSE also supports other physician and community education activities including the annual Hippocrates Society lecture, the Greater St. Louis Science Fair, World Food Day, the Missouri Physicians Health Program, and the SLMMS Alliance.

## SLMMS Alliance

The Alliance plays an integral part of fulfilling the SLMMS mission through community health education, charitable projects and legislative advocacy. Their membership includes physician spouses, medical residents and students, and friends of physicians. Alliance members present health education programs in area schools, and their Voices of Excellence program challenges middle school students to improve their public speaking skills. Throughout the year, the Alliance raises funds for non-profit charities such as St. Martha's Hall, Nurses for Newborns ,and others. They also provide scholarships for area medical students, and advance the Society's legislative agenda through their annual advocacy day at the Missouri State Capitol.

## Maintaining Relevance

As a membership driven organization, SLMMS constantly works to remain relevant for its physician members. SLMMS regularly provides e-news updates with news and announcements, and earlier this year, launched Facebook and Twitter social media platforms through the efforts of President Cabbabe.

But ultimately, it all goes back to preserving autonomy and maintaining the physician-patient relationship. SLMMS believes physicians need to remain as the driving force to make that happen.

"Physicians are indispensable members of society," said Dr. Cabbabe. "Over the course of our 180 years, medicine has prospered under the leadership of physicians, and it's our responsibility to preserve that role. Organized medicine assists us in accomplishing this task. It is our duty to educate all physicians and non-physicians about what organized medicine has achieved and why it must persist – for our patients and our communities." **MM**

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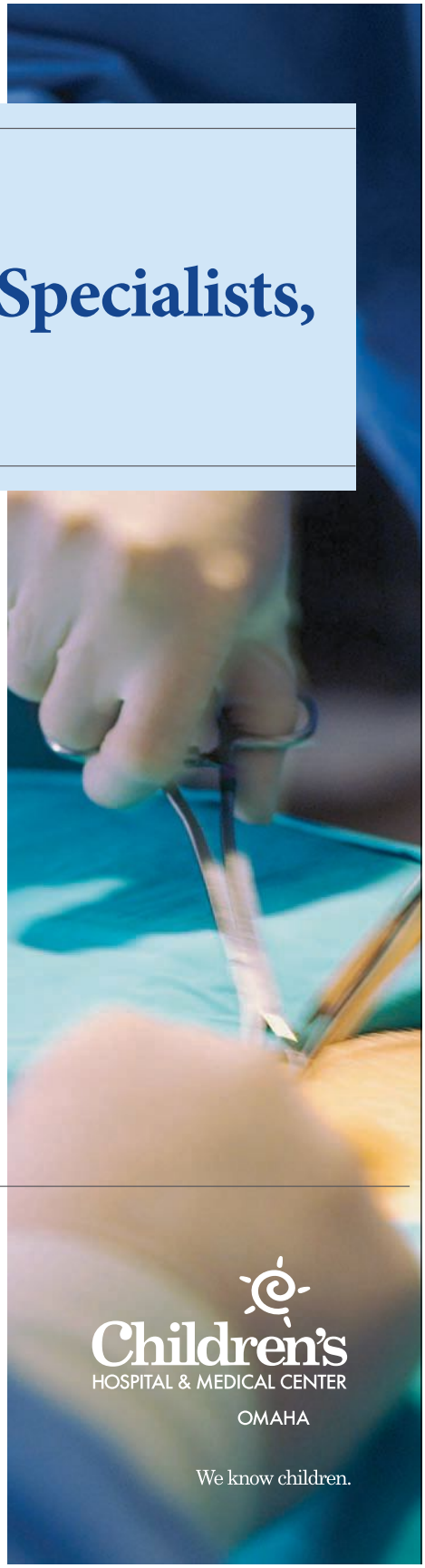
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# State of the School of Medicine

*by Philip O. Alderson, MD*

## SLU Goals: grow and evolve our clinical practice, recruit strong new academic and research leaders, and build on the quality of student life on campus.

I last reported to *Missouri Medicine* on the state of the Saint Louis University (SLU) School of Medicine in 2011. Since that time, with the support of a productive faculty and staff, we've been able to grow and evolve our clinical practice, recruit strong new academic and research leaders and build on the quality of student life on campus.

What many would regard as the most significant advance at SLU is one of the most recent. On September 1, 2015, following two years of confidential negotiations, a three-way transaction was completed that allowed SLU to reacquire SLU Hospital from the Tenet Corporation and immediately transfer the hospital to the ownership of the St. Louis portion of the Sisters of St. Mary system (SSMSTL). In return for this transfer, SLU received two positions on the board of directors of SSMSTL and received a minority equity stake in the corporation.



Philip O. Alderson, MD, MSMA member 2009, is Dean, School of Medicine and Vice President, Medical Affairs, at Saint Louis University.
*Contact: palderso@slu.edu*

The national publication Becker's Hospital Review rated it as the most interesting healthcare transaction in the nation in 2015. This transaction put SLUH, which now is known as SSM Health -Saint Louis University Hospital, at the tertiary-quaternary apex of an eight-hospital regional network that also contains many SSMSTL outpatient centers.

The early returns from this new partnership are positive. SSM is bringing its mission-driven and quality-driven hospital management style to SLUH. SLUH sits adjacent to the Cardinal Glennon Children's Medical Center, which also is an SSM hospital. This provides the SLU campus with a unified hospital vision and partner for the first time in decades. Over the next five years, SSMSTL is committed to invest in new building and renovation projects including a new mainframe adult hospital and a new outpatient ambulatory care center on the Grand Boulevard campus. Over the past three years, SLU has managed to acquire the land and properties north of the current hospital location all the way to Chouteau Avenue. This provides an excellent area in which to develop what will be the new Grand Avenue medical center. Although our clinical practice, SLUCare, remains contractually independent of SSMSTL, it is rapidly becoming deeply integrated into the SSMSTL regional network. We're optimistic that our patients, students, faculty and community will be the ultimate beneficiaries of this exciting new partnership.

Over these past several years many new academic leaders have been recruited to SLU's School of Medicine. One of them is Dr. Tom Burris who came to

SLU from Scripps Florida in 2013 to lead our department of pharmacology and physiology. Since his arrival at SLU, Dr. Burris has received multiple new NIH R01 grant awards in his primary area of investigation, which is nuclear receptor biology. Dr. Burris has recruited several outstanding people to join him at SLU. He and his team are pursuing nuclear receptor science in cancer, neurodegenerative disease, autism, and a variety of other disorders.

Dr. Dan Hoft, a productive SLU faculty member who is nationally respected for his work on tuberculosis and other infectious diseases, stepped in upon the retirement of Dr. Bob Belshe and now leads SLU's Infectious Diseases group and the Vaccine Trial and Evaluation Unit (VTEU) where he works closely with Dr. Sharon Frey. About two years ago the VTEU was renewed by the NIH as one of nine vaccine development units in the nation and more recently was designated as one of only two of the VTEUs that will serve to develop the "_omics" components (proteomics, genomics, metabolomics, etc.) of vaccine trial and development work for the other VTEUs. Dr. Hoft also received a recent multimillion dollar award from the Gates Foundation to pursue his development of a vaccine for multi-drug resistant tuberculosis.

When Dr. Rick Lee, a noted cardiovascular surgeon, joined SLU from Northwestern three years ago, we merged the division of cardiology, which was in internal medicine, with cardiovascular surgery, a division within the department of surgery. This created a new fiscally independent operational unit known as the Center for Comprehensive Cardiovascular Care ("C-4"). C-4 is seeing much higher volumes of patients than before the merger and is providing state of the art interventional and surgical approaches to patients with atrial fibrillation, valvular heart disease and many other cardiac conditions.

The departments of neurology and psychiatry, which had been a single joint department for nearly 10 years at SLU, once again are independent. These disciplines are independent at virtually all other American medical schools. They merged at SLU at a time when such mergers seemed like a new and innovative way to move ahead. Over the years, most other schools who tried this approach eventually returned to independent departments. Dr. Henry Nasrallah, who we recruited from the University of

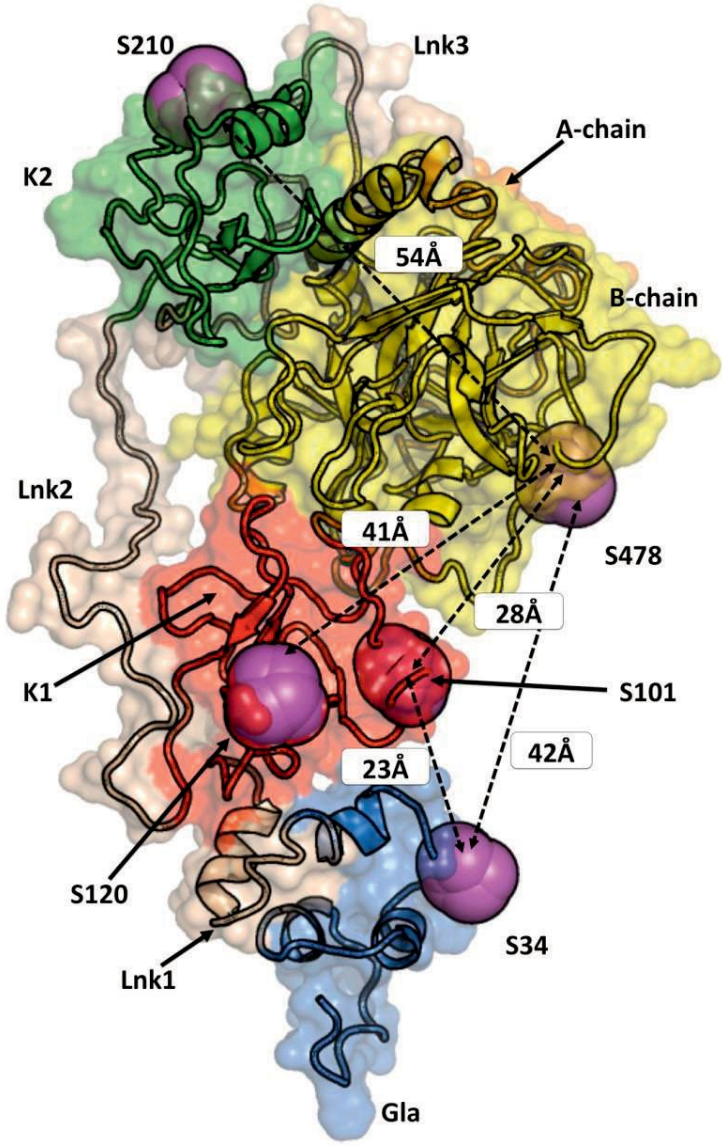



**Figure 1**
X-ray crystal structure of the vitamin K-dependent coagulation factor prothrombin showing the spatial arrangement of the Gla domain (Gla), two kringles (K1, K2), protease domain with the A chain (Ac) and catalytic B chain (Bc) and three linkers connecting the Gla domain to kringle-1 (Lnk1), the two kringles (Lnk2) and kringle-2 to the A chain (Lnk3). The structure was validated by single molecule FRET (smFRET) measurements using probes (spheres) introduced in various domains. X-ray crystallography and smFRET equipment are state-of-the-art resources in the Department of Biochemistry and Molecular Biology.

Cincinnati three years ago, initially led the joint department and then facilitated the return to separate departmental status. He now chairs the department of psychiatry. The department of neurology has interim leadership through Dr. Sean Goretzke, head of the division of pediatric neurology. This new alignment occurred only months ago and is off to a solid start.

The School of Medicine's funded research portfolio is growing, with especially notable contributions in structural biology. Dr. Enrico Di Cera, who joined SLU as chair of biochemistry nearly five years ago, published recently his group's excellent work showing for the first time the molecular structure of prothrombin (See Figure 1). In 2016, Dr. Duane Grandgenett, a long-time SLU professor who first described the critical enzyme integrase over 30 years ago, published in Nature with colleagues from the University of Minnesota and Cornell, the first demonstration of the molecular structure of the intasome of the retrovirus known as Rous sarcoma virus (RSV). This structure is critical to understanding HIV integration into human cell DNA (Figure 2), and will help guide the development of new anti-HIV drugs.

Drs. Burris and Di Cera working together with SLU's department of chemistry have put together a program that has allowed SLU to purchase a 700 MHz nuclear magnetic resonance (NMR) instrument that will be housed on SLU's main campus. Together with our powerful x-ray diffraction capabilities and single molecule analytic techniques in Dr. Di Cera's lab, this new NMR will allow SLU to have a state of the art Structural Biology Program. The NMR is expected to be fully operational within a year.

Because our ultimate goal as a medical school is to teach and develop great physicians, I save for the last the work being done in these areas. In 2015, Dr. Angela Sharkey, associate dean for faculty affairs and development, created the School of Medicine's first Academy of Educators. The Academy is designed to honor the school's very best educators – those who have received other school-wide or departmental teaching awards, not once or twice, but repeatedly during their careers. We expect this honor to be reserved for no more than one to two inductees per year. One of the five inaugural inductees to the Academy was Dr. Stuart Slavin. Dr. Slavin, who is our

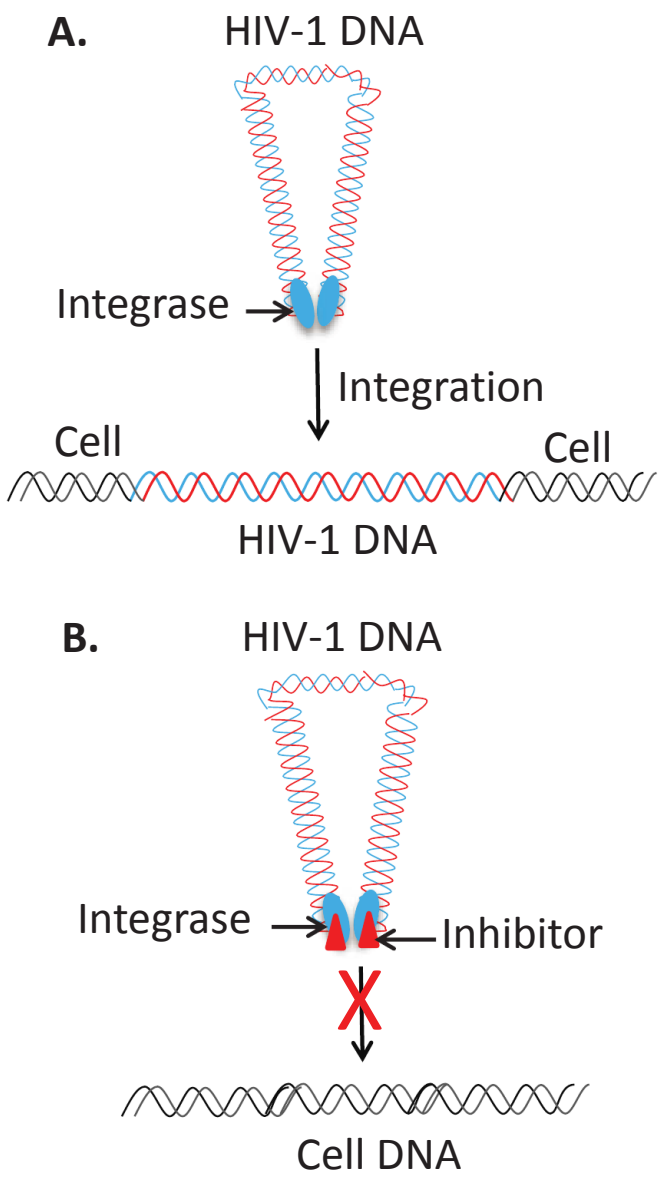



**Figure 2**
Integration of HIV-1 DNA into cell DNA. A. The HIV-1 integrase (blue oval) inserts the viral DNA into human cell DNA producing a permanent copy of the viral DNA in the genome. The integrated HIV-1 DNA subsequently produces more virus particles to infect other human cells. B. Integrase inhibitors (red triangles) prevent the integration of the viral DNA and thus stops virus replication. There are three FDA approved integrase inhibitors which are used in combination with different inhibitors that block other viral proteins thus preventing HIV-1 replication. Combinational drug therapies help prevent drug resistance.

associate dean for curriculum, has been working to improve student well being and the organization of the SLU curriculum over the past several years. These improvements focus on the pre-clinical years and include a true pass-fail approach, shortening and moving the Anatomy course later in the first year curriculum, developing substantial time for student electives in the first and second year and beginning the phase three clinical year in April of the second year. These structural changes have been well received, but are only part of the story. By providing more personal attention to students and working on student formation (Figure 3), Dr. Slavin and his colleagues strive to develop great physicians who have the resiliency to cope with the high stress existence of a medical student and physician. The results of Dr. Slavin's work have been widely cited and show that the frequency of anxiety and depression among SLU medical students has declined dramatically. In addition, the new national AAMC survey of second-year student satisfaction and attitudes, published for the first time in February, 2016, shows that SLU students have significantly more positive feelings about their time in school, their approach to patients and their future careers than the national averages derived from a composite of all other schools. We are heartened to see these new results, and are encouraging Dr. Slavin and his colleagues to continue this outstanding work.



**Figure 3**
Stuart Slavin, MD, with six SLU medical students on the SLU medical campus.

I'm delighted to be able to report these activities at SLU and will watch eagerly to see how the school and medical campus evolve over the years ahead. I will not, however, do that as the dean of the school. A few months ago I approached President Fred Pestello and indicated that I believed it was the right time to begin the process of searching for my successor. I am proud to have served as the dean at SLU for eight full years as this article goes to press. God willing, I will continue to serve until my successor is appointed through a national search process that now is underway. It has been a great pleasure to work with the outstanding faculty and staff of this medical school and especially our wonderful students during my eight years here at SLU. I know that our faculty leaders and my successor will lead the SLU School of Medicine to great levels of achievement in the years ahead. **MM**

SAINT LOUIS UNIVERSITY

# Rheumatology Update: 2016

*by Terry L. Moore, MD*

The Adult Division of Rheumatology at Saint Louis University (SLU) was founded in 1955 by Jack Zuckner, MD, and the Pediatric Division in 1968. Dr. Zuckner stepped down from being Division chiefs in 1983. Since then, over the past 32 years, Terry Moore, MD, has been Division chiefs, and the faculty has grown to six full-time MDs and three PhDs.

The Division has trained more than 60 Rheumatologists who practice in academic and private practice settings all over the world. The Division has received multiple research grants from the National Institutes of Health (K and RO 1 awards) and private organizations for their studies in juvenile idiopathic arthritis, rheumatoid arthritis, and systemic lupus erythematosus. These studies have resulted in more than 200 publications and 225 presentations at international meetings.

The Rheumatology Divisions at SLU are multidisciplinary in nature and see over 9,000 patients a year. The following articles emphasize practical topics in Rheumatology which should provide the primary physician with insight into these common problems.

Dr. Moore's article provides a summary of how to evaluate a patient with possible autoimmune disease. Katherine Temprano, MD, describes Raynaud's and its ramifications. Rama Bandlamudi Atluri, MD, shows how to evaluate and treat inflammatory myositidies. Reema Syed, MD, addresses how to evaluate rheumatological causes of the limping child. Peri Hickman Pepmueller, MD, describes how to evaluate overlap and undifferentiated connective tissue diseases. These articles provide a basic approach to many common rheumatological problems a primary care physician may come across. **MM**



Terry L. Moore, MD, FACP, FAAP, MACR, is the Director, Division of Adult and Pediatric Rheumatology, Professor of Internal Medicine, Pediatrics, and Molecular Biology and Immunology at Saint Louis University School of Medicine and SSM Cardinal Glennon Children's Hospital.
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# Laboratory Studies in Autoimmune Diseases

*by Terry L. Moore, MD & Austin M. Dalrymple, DO*

**We present laboratory studies that will provide the primary care physician with the necessary information to determine if a further autoimmune diseases work-up is indicated.**



Terry L. Moore, MD, FACP, FAAP, MACR, is the Director, Division of Adult and Pediatric Rheumatology, Professor of Internal Medicine, Pediatrics, and Molecular Biology and Immunology at Saint Louis University Medical Center and SSM Cardinal Glennon Children's Hospital. Austin M. Dalrymple, DO, is Senior Fellow, Pediatric Rheumatology, at Saint Louis University Medical Center and SSM Cardinal Glennon Children's Hospital.
*Contact: mooretl@slu.edu*

## Abstract

**Autoimmune diseases (AID) are a great percentage of the patients needing to be seen by Rheumatologists. Their initial work-up by their primary care physician (PCP) can be helpful in determining who needs to be seen in consultation. If interpreted properly, initial laboratory studies can help the PCP know when to initiate a consultation. The following laboratory studies as outlined will provide the PCP with the necessary information to determine if a further AID work-up is indicated.**

## Introduction and General Studies

There are general laboratory studies which can indicate the possibility of an underlying AID. These include the complete blood count (CBC), urine analysis (UA), sedimentation rate (ESR), C-reactive protein (CRP), comprehensive metabolic panel (CMP), and muscle enzymes. In the CBC, we are looking for an anemia of inflammatory disease which can develop. In active inflammatory diseases, absorption of iron is limited and not distributed to the bone marrow resulting in a chronic anemia unless the inflammation is controlled. We also look for acute falls in hemoglobin and hematocrit, mainly seen in patients with systemic lupus erythematosus (SLE) or Sjogren's Syndrome (SS). They have developed autoantibodies to red cells. The most common cause of leukopenia and thrombocytopenia is due to an autoimmune disease with the development of anti-white cell and anti-platelet antibodies in these patients causing peripheral destruction.

Urinalysis as a screen is self-evident. Acidic pH, proteinuria, red cells, white cells, and red cell casts are all evidence of possible autoimmune renal damage. If the UA is abnormal, a 24-hour urine for creatinine clearance and total protein is ordered. If abnormal, a renal biopsy is indicated to determine etiology and possible therapy.

General inflammation is monitored by ESR and should be less than 15 mm/hr. CRP should be $<0.3$ mg/dl and ideally $<0.1$ mg/dl. Values out of this range may indicate a possible inflammatory process and need for further work up.[1]

The CMP findings are again fairly self-evident. Increased creatinine indicates renal disease, increased liver enzymes, a possible hepatitis or drug reaction, and increased muscle enzymes, a possible myositis. It is emphasized that all patients with possible myositis should have all three muscle enzymes (creatinine phosphokinase (CPK), aldolase, lactic dehydrogenase (LDH)) evaluated. One thing we emphasize is in different genetic populations normals can be different. African-Americans have

a higher normal CPK, between 200-400 IU. Caucasians and Asians should be less than 200 IU, but, CPK is a very sensitive assay. Exercise can elevate CPK in many patients. Aldolase and LDH are not affected and can be relied on to complete an evaluation of myositis. Neopterin and von Willebrand's Factor Antigen can, also, be measured. One thing that is most misunderstood in the CMP is the albumin/ globulin ratio. Albumin should be around 4 g/dl and globulin 2.5 g/dl, so the ratio should be around 1.6 normally. If that ratio is closer to 1 or less than 1 then you have a reversal of the albumin/globulin ratio and possible hypergammaglobulinemia. This is usually the first evidence that there may be an underlying inflammatory process or a patient with an autoimmune disease. These are the screening tests and thought processes that should be entertained to determine a more definitive work up.[2]

A more definitive work up for AID includes rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibodies , antinuclear antibodies (ANA), complement levels, antiphospholipid (APLS) antibodies, anti-neutrophilic cytoplasmic antibodies (ANCA), and genetic studies.

## Rheumatoid Factor

The RF that is measured by most assays is a 19S IgM molecule; however, RFs are found in all immunoglobulin classes. It is found in a higher percentage of rheumatoid arthritis (RA) patients, about 80-90%, but can be seen in all connective tissue diseases. By definition, it is an anti-IgG globulin that binds to the Fc fragment of IgG forming an immune complex. By enzyme-linked immunoabsorbent assay (ELISA), an abnormal level is > than 20 IU, but normally RA patients are > 40 IU. About 10-30% by ELISA depending on the sensitivity are positive in juvenile idiopathic arthritis (JIA) patients, and about one-third of patients with SLE and scleroderma (SSc) are positive for RF; however, about 80% of patients with SS are positive. There are a multiplicity of viral infections that cause transient RF positivity including the Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus, and hepatitis B and C. These are usually negative for αCCP antibodies. RF also can be found in extravatory fluids. In fact, when you look at extravatory fluids, synovial, pleural, and pericardial fluid, these fluids have a high propensity for immune complex formation, so you are going to find autoantibodies in the extravatory fluids in higher concentrations than in the peripheral blood.[3]

## Anti-Cyclic Citrullinated Peptide Antibodies

The second antibody that we assay for in RA seems to correlate better with disease and is called αCCP antibodies. These are antibodies that are reactive with synthetic peptides containing the amino acid citrulline, the most translationally modified arginine residue found in approximately 75-80% of adult RA patients. Testing in most assays is only for the IgG antibody to CCP. Studies in Sweden have shown that they may appear many years before actual disease.[3]

## eTa Protein

Recently, a possible new inflammatory marker has been identified. They are called 14-3-3 eTa proteins, ubiquitously expressed intracellular isoforms. These isoforms are expressed in inflammatory processes and are detected mainly in RA and in psoriatic arthritis.

## Antinuclear Antibodies

ANA positivity is a common cause for referral to Rheumatologists. ANA are a diverse collection of antibodies directed against numerous macromolecules which are normal constituents of the cell nucleus. ANA presence are a hallmark of AID, but not diagnostic. About 30% of the healthy female population will be ANA positive. If positive, then an ANA profile is indicated to determine the exact antibody causing the ANA to be positive. Again, immunogenic viruses such as EBV, CMV, and parvovirus can cause a transiently or permanently positive ANA. Also, each year we see probably five to ten patients referred to us with a positive ANA that have autoimmune thyroiditis with antibodies to thyroperoxidase (TPO) or thyroglobulin. ANA are a screening test. It can define a specific AID, but titers, rising or falling, are not associated with disease activity. However, some autoantibodies may define rises and falls in disease activity.[4]

The most widely used technique for the detection of ANA is immunofluorescence (IF) using human epithelial cells (Hep-2). These cells have abundance of double (ds) and single-stranded (ss) DNA, histones, Sm, RNP, Scl-70, and SS-B substrate, but a very low concentration of antibodies to SSA or cytoplasmic antigens. Therefore, even if the ANA is negative, if SS is suspected, antibodies to SSA should be run. By IF, five patterns are generally described. The homogenous pattern which is very nonspecific, the speckled pattern which is produced by a multitude of antigens, the rim pattern, the nucleolar pattern which is usually found in patients with scleroderma and scleroderma dermatomyocitis overlap, and the fifth pattern is discreet speckled which is what we see with antibodies to centromere. If the IF ANA is positive, an ELISA profile for the specific antibodies is needed. Most profiles will contain antibodies to dsDNA, SSA, SSB, Sm, RNP, and chromatin.

They may not contain antibodies to Scl70, histones, Jo-1, RNA polymerase III, centromere, and lesser antibodies. You may have to ask for a specific assay or ELISA for those.[5]

## Autoantibodies in SLE

ANA should be positive in 100% of SLE patients by one method. Antibodies to dsDNA occur in about 75% of patients. These are the patients that have high incidence of renal disease, central nervous system (CNS) disease, vasculitis, and low complement levels. In most patients, these levels will rise and fall with active disease. There are two assays for antibodies to dsDNA. There is the ELISA assay which is sensitive but it can give positive results for ss DNA. It can also cause false positivity with certain drugs, hepatitis B and C,etc.. High titers are very specific for SLE. The most specific assay is IF with Crithidia luciliae substrate. It is completely specific for dsDNA antibodies. High titers are very specific for SLE and correlate with very active disease.[5]



Laboratory studies as outlined in this article will provide the PCP with the necessary information to determine if a further autoimmune diseases work-up is indicated.

Other autoantibodies include antibody to chromatin, antibodies to nucleosomes, which occur in about 75% of patients. These are also patients who usually have renal disease. Antibodies to chromatin may occur with antibodies to histones in drug-induced syndromes, especially associated with oral contraceptives of high estrogen content, propylthiouracil, and some of the hypertensive medications. A more specific antibody that is part of the criteria for SLE, are antibodies to Sm and occurs in about 30-40% of patients. This antibody correlates with pleural or pericardial disease, so if antibody to Sm is positive, screening with baseline pulmonary function tests (PFTs) to look for restrictive lung disease and an echocardiogram to look for pulmonary hypertension (PAH) is indicated and repeated in two year intervals. The other antibody with the same association is antibodies to RNP. This is the antibody by itself that we define mixed connective tissue disease (MCTD). This antibody alone may correlate with milder disease or less renal disease. These are the patients with high incidence of Raynaud's, myositis, and can have restrictive lung disease and PAH. Antibodies to SSA or Ro and antibodies to SSB or La are the antibodies we find in 30 to 60% of SLE patients. These are the antibodies seen with subcutaneous lupus and are the antibodies that cross the placenta and bind to the fetal conduction system. The fetus can have neonatal lupus. These are the patients who have dry eyes and dry mouth (sicca complaints) and have a high incidence of partial C2 and C4 deficiencies. Lastly, there is a cytoplasmic antibody called anti-ribosomal P which does correlate in certain cases with CNS vasculitis.[6]

## Autoantibodies in SS

The majority of patients (90%) with SS have antibodies to SSA and/or SSB. They again correlate with the presence of vasculitis, leukopenia, thrombocytopenia, and positive RF. These are the antibodies associated with anti-white cell and anti-platelet antibodies and hypergammaglobulinemia. Seven to ten percent of these patients may have an underlying B cell hyperproliferative syndrome and so at baseline, measure IgG levels. IgG levels over 2,000 mg/dl at baseline may indicate a propensity for developing a B cell lymphoma. Anti-SSB antibodies are usually associated with anti-SSA antibodies. Anti-SSB antibody by itself may indicate an underlying lymphoproliferative disease.[5, 6]

## Autoantibodies in Polymyositis (PM)/ Dermatomyositis (DM)

There are multiple antibodies in PM/DM. These are anti-synthetase antibodies. The most common is anti-histidyl tRNA synthetase antibody (anti- Jo-1). It occurs in about 40% of patients with PM/DM. It is also associated again with restrictive lung disease, so these patients need PFTs and followed very carefully. There are a multiplicity of other autoantibodies which can be defined by a myositis panel which include antibodies to PL-7, PL-12, OJ, EJ, SRP, Zo, KS, Mi2, SAE,TIF1-¥, NXP2, and Ha. A small percentage of patients have each of these, but their presence is very specific for an underlying autoimmune myositis. Myositis-associated interstitial pneumonitis can be found in 95% of patients that have antibodies to PL-12, KS, and OJ. Arthritis, Raynaud's, fever, mechanic hands, Gottron's papules, and heliotropic rash have a high association with

the presence of anti-Jo-1 and PL-12 antibodies. There is also an anti-HMGCoA antibody which we mainly see in patients with statin induced myositis.[7]

## Autoantibodies in SSc

There are three more common antibodies found in SSc, anti-centromere, anti-topoisomerase (Scl70), and anti-RNA polymerase III antibody. Anti-centromere antibody is usually found in limited scleroderma (CREST). They form the discreet speckled pattern ANA. This form is not benign with a good percentage of these patients developing PAH. Therefore, these patients with anti-centromere antibody should also be followed closely with PFTs, echocardiogram, and possibly right heart catheterization if there is evidence that the pulmonary artery pressure is greater than 35 mmHg on estimate from echocardiogram. Antibodies to Scl70 and RNA polymerase III are associated with a, sclerodactyly and diffuse skin involvement. A high incidence of these patients develops restrictive lung disease. So, PFTs and echocardiogram need to be followed. The importance of the antibody to RNA polymerase III to clinicians is there is a high incidence of the patient having an underlying cancer. Therefore, cancer screening has to be emphasized. Chest x-ray, mammograms, pelvic, and pap smear, and colonoscopy have to be up to date on any of these patients with antibody to RNA polymerase III. The other antibodies to PM-Scl, fibrillarin, high nuclear RNP1, etc., are found in a small percentage of patients.[8]

Overall, specificity of ANA presence in AID in SLE are antibodies to dsDNA, Sm, RNP, SS-A, and SS-B, antibodies in MCTD, are specifically antibodies to RNP alone, antibodies in SSc to centromere, topoisomerase I (Scl70), and RNA-polymerase III, antibodies in PM/DM are antibodies to Jo-1, etc., and in SS antibodies to SS-A and SS-B. One needs to look at these and then make a specific diagnosis. Many times it's more important to actually know what antibody is present than specifically making a specific disease diagnosis because many of these antibodies define what organ systems are involved. These include antibodies to dsDNA in renal disease and vasculitis, antibodies to Sm/RNP/centromere/Jo1/RNA polymerase III, and Scl70 for pulmonary and pleural involvement, and antibodies to SS-A and SS-B for sicca complaints and hypergammaglobulanemia.[5]

## Complement Measurement

Measuring disease activity directly is difficult, because none of the assays give direct disease measurement, just indications. These are immune complex diseases, but the immune complex assays available are not very helpful. We do use complement protein measurements to aid in defining activity of disease. Immune complexes fix complement; and, therefore, we may see a fall in complement proteins. Three complement pathways are present, the classical, mannose binding lectin, and the alternative pathway. Most of the time in our AID, we are dealing with the classical pathway. We mainly assay for CH50, C4, and C3. C4 is the rate limiting step of the classical pathway and therefore it falls quicker and is more sensitive to immune complex activation. However, you need to know the genetics. There are four alleles coding for C4, two for C4A and two alleles for C4B. Knowing the genetic make-up will determine if low C4 levels are significant. Measuring C3 can give you information on all three pathways. Measuring CH50 gives you a picture of the whole pathway to screen to rule out complement deficiencies. If you have a low CH50 with a normal C3 and C4 then you have evidence of a complement deficiency. You then measure each component separately to determine the deficiency. About 1.9% of the population has a partial C2 deficiency and about 0.7% of the population has a partial C4 deficiency. Partial C4 deficiencies are present in a high number of SLE patients.[9,10]

## Anti-Phospholoipid Antibodies

Any patient evaluated with AID, we want to define whether there is any underlying anti-phospholipid syndrome (APLS). Many patients with SLE may also have associated APLS, but APLS can also be primary. Measuring anti-cardiolipin antibodies, lupus anti-coagulant, and anti-beta 2 glycoproteins on a fasting specimen is required. The IgG antibody of the three is associated with more clotting abnormalities and symptoms of migraine headaches and miscarriages in the family. The presence of these antibodies can cause problems with pregnancy, so you want to counsel any young female about these antibodies before they become pregnant.[11]

## Anti-Nuclear Cytopasmic Antibodies (ANCA)

We now have assays (IF and ELISA) that can screen for vasculitidies, such as granulomatosis with polyangiitis (GPA) and microscopic polyarteritis (mPA). There are two types of ANCAs by IF; cANCA which is cytoplasmic ANCA and pANCA which is perinuclear ANCA. cANCA are antibodies to proteinase 3 (PR3) which is seen in about 90% of patients with GPA. In most patients with GPA, it can be correlated with disease activity. These antibody levels will rise and fall with disease activity. pANCA is antibody to myeloperoxidase (MPO). These are antibodies

seen in eosinophilic GPA, microscopic polyarteritis, a small percentage in inflammatory bowel patients, and in drug-induced syndromes, especially in patients on minocycline or thyroid patients on propylthiouracil.[12]

## Genetic Studies

These studies can be helpful in evaluating young adults for seronegative spondyloarthritides. In ankylosing spondylitis about 90% of those patients will be positive for HLAB27. Those with enthesitis-related arthritis will be positive in about 85% of cases. A smaller percentage of inflammatory bowel disease and those with psoriatic arthritis will be positive, especially those with spinal involvement. HLAB51 positivity can be found in about 60% of patients with Behcet's.[13]

## Additional Studies

What other studies can be helpful? In patients that have peripheral vasculitis, you may want to measure cold precipitable proteins or cryoglobulins. The problem is that many labs do not perform this assay correctly. The blood has to be drawn in a tube that is at 37 degrees or body temperature. After drawing the blood, it has to be placed in a 37 degree water bath to clot, the serum aspirated, and then placed at 4 degrees and observed. If a precipitate forms, a cryoglobulin is present and is very specific for immune complex presence. There are three types of cryoglobulins, monoclonal, mixed, and polyclonal. What we look for in AID disease are the mixed or polyclonal. Also, about 20 % of patients with hepatitis B and C will be positive for cryoglobulins.

## Organ Evaluating Studies

Skin biopsies may help define an immune complex disease, a 24-hour urine for creatinine clearance and total protein spillage may determine if a renal biopsy is needed, PFTs for restrictive lung disease, echocardiogram for PAH, and barium swallow for esophageal problems may be helpful to evaluate specific organ disease. The skin biopsy may show a lympho-proliferative response by H&E staining. IF studies for immunoglobulin and complement deposition are more specific for immune complex deposition. Immune complex renal disease in SLE is defined by IF studies showing immunoglobulin and complement deposition on the biopsy, which will determine severity and the future medical regimen.

## Synovial Fluid

A normal synovial fluid is straw colored, transparent, very viscous with <200 WBCs/mm. In inflammatory arthritis, such as RA, you are going to see cloudy fluid, less viscous because of the inflammation, and the white count is going to be anywhere from 2,000 to 100,000/mm. In trauma, you may see straw to bloody-grayish fluid, transparent, and viscosity is high because of not many inflammatory cells, mainly red cells. Septic fluid is going to be bloody and it's going to be turbulent, very low viscosity, and the white count usually will be greater than 20,000/mm, but gram staining the fluid and cultures are indicated to define further. Pseudogout and gout are going to produce an inflammatory fluid with low viscosity and crystals are to be evaluated by polarizing microscope. [14]

Overall, these outlined studies will provide an excellent evaluation of a patient for AID, and provide information to provide a correct diagnosis and help in determining a therapeutic regimen for the patient.

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## Disclosure

None reported. **MM**

# A Review of Raynaud's Disease

*by Katherine K. Temprano, MD*

**Raynaud's syndrome is a relatively common phenomenon and patients should be referred promptly to a rheumatologist to assist with differentiation between primary and secondary Raynaud's.**



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## Abstract

**Raynaud's phenomenon is a relatively common but often unrecognized clinical syndrome causing characteristic color changes in the digits as a result of vasospasm. This may occur after exposure to a cold environment, emotional stress, or from other physical or medication exposures. Differentiating between primary and secondary Raynaud's is important as secondary Raynaud's can be complicated by digital ischemia and gangrene whereas primary Raynaud's is generally a benign condition. Referral to a rheumatologist is recommended to help evaluate for an underlying rheumatologic condition and to guide future therapy.**

## Epidemiology

Community-based surveys estimate Raynaud's may be present in 5-20% of women and in 4-14% of men. The prevalence in individuals over age 60 is 0.1-1%.[1] Primary Raynaud's is generally considered a benign condition and typical age of onset is from 15 to 30 years of age. This tends to be more common in young females and can be familial.[2] Primary Raynaud's may remit over time. A prospective study over seven years in a middle age Caucasian white population found remission occurred in 64% of women and men although some symptoms remained in about 20% of those labeled as remission.[3]

## Clinical Presentation

Raynaud's phenomenon is classically described with a triphasic color change of the digits with initial white or pallor (ischemic phase), then blue or cyanosis (deoxygenation phase), followed by red or erythema (reperfusion phase). Screening questions should include:

1) Are your fingers unusually sensitive to the cold?

2) Do your fingers change color when they are exposed to cold temperatures?

3) Do they turn white, blue, or both?

Generally, the diagnosis of Raynaud's is confirmed if there is a positive response to all three questions.[4] Then, if positive for the diagnosis of Raynaud's, further evaluation should occur to differentiate between primary and secondary Raynaud's. It is typically present in the hands but can also affect the toes, nose, earlobes, or nipples. It may begin in one finger and spread symmetrically to other digits, often sparing the thumb.

A typical attack may last less than an hour but can also persist for hours. In primary Raynaud's, attacks are more likely symmetric, episodic, and without evidence of peripheral vascular disease. Patients more commonly have a negative ANA and normal inflammatory markers. There should be no evidence of tissue gangrene, digital pitting, or tissue injury in primary Raynaud's. In contrast,



**Figure 1**
Screening questions for Raynaud's should include:
1) Are your fingers unusually sensitive to the cold?
2) Do your fingers change color when they are exposed to cold temperatures?
3) Do they turn white, blue, or both?
Generally, the diagnosis of Raynaud's is confirmed if there is a positive response to all three questions.
*Source: http://www.nhlbi.nih.gov/health/health-topics/topics/raynaud/*

patients with secondary Raynaud's will describe attacks that are more frequent, painful, often asymmetric and may lead to digital ulcerations. These ulcerations can resolve to leave scars or digital pits, or may progress to more severe digital necrosis, gangrene, or auto-amputation. Digital ulcerations can become secondarily infected, leading to osteomyelitis, and can require surgical intervention. Clues that may raise concern for secondary Raynaud's include age of onset greater than age 40, male gender, digital ulcerations, asymmetric attacks, ischemic signs proximal to the fingers and toes, and abnormal nailfold capillaroscopy. Nailfold capillaroscopy is an inexpensive, quick, and non-invasive exam technique that can help differentiate primary from secondary Raynaud's. Lubricant is placed on the nailfolds and the nailbed capillaries can be viewed using an ophthalmoscope set at 10 to 40 diopters. The fourth and fifth digits have the greatest translucency of the skin but all fingers should be visualized.

Early abnormal findings will include few capillary hemorrhages and few enlarged capillaries. A more active pattern may show moderate loss of capillaries, frequent giant capillaries, and disorganized vascular architecture. A late pattern may show "drop-out" with severe loss of capillaries with extensive avascular areas and ramified or bushy capillaries. These abnormalities are found in patients with underlying connective tissue diseases such as systemic sclerosis, dermatomyositis, or undifferentiated connective tissue disease. In a study of 586 patients with Raynaud's followed for 3,197 patient years, systemic sclerosis developed in 25.8% of patients with abnormal capillary pattern, in 35.4% of those with a specific autoantibody, and in 79.5% of those with both abnormal nailfold capillaries and a specific autoantibody. Patients with both predictors were 60 times more likely to develop systemic sclerosis than in those with neither.[5]

## Disease Associations

Raynaud's is often the presenting symptom for numerous connective tissue diseases such as scleroderma, lupus, or mixed connective tissue disease. Thus, early on, many patients are thought to have primary Raynaud's; however, a meta-analysis of 640 patients with primary Raynaud's found that 13% eventually developed into a connective tissue disease.[6] Another study showed 15-20% of patients with Raynaud's who had autoantibodies, abnormalities of nail fold capillaries or both and who did not initially meet criteria for connective tissue disease developed into a defined connective tissue disease typically within two years.[7] Further investigation is warranted to look for an underlying cause. Etiologies may be due to vasospastic, structural, or hematologic causes. Vasospastic causes may be drug-induced (ergot, methysergide, beta-blockers, dextroamphetamine, methylphenidate, bleomycin, cisplatin, clonidine, cocaine, cyclosporine, interferon-alpha, nicotine, and vinblastine). Other vasospastic causes include pheochromocytoma, carcinoid syndrome, or thyroid disease. Structural causes are numerous and may include thoracic outlet syndrome, atherosclerosis, brachiocephalic trunk disease as in Takayasu's arteritis, Buerger's disease or thromboangiitis obliterans, cold injury, connective tissue diseases, polyvinyl chloride, use of vibratory tools such as jackhammers, or angiocentric lymphoma. Hematologic causes include cryoglobulinemia, cryofibrinogenemia, paraproteinemia, or polycythemia. Mimickers of Raynaud's include other vascular disorders such as acrocyanosis and erythromelalgia. Acrocyanosis typically lacks the triphasic color change but can cause a more persistent blue-red discoloration of the skin of the hands and feet after cold exposure. It is more common in females but is painless. Erythromelalgia also occurs more commonly in females but is exacerbated by heat exposure and leads to pain in the feet and lower limbs, and less commonly, the hands.

## Pathophysiology

Raynaud's phenomenon was first described in 1862 by Maurice Raynaud and was described as "local asphyxia of the extremities" which was a result of "increased irritability

of the central parts of the cord presiding over vascular innervation." Over a century later the pathophysiology is still not perfectly understood. There are likely numerous factors involved in the pathogenesis of Raynaud's, such as vascular, intravascular, and neural abnormalities, and these factors may differ among those with primary versus secondary Raynaud's. Digital arteries constrict more strongly with people with Raynaud's compared with those without Raynaud's. Capillaries provide nutrients to the skin but there is also a rich concentration of arteriovenous anastomoses in the fingers and toes that function in thermoregulation. In two small studies (12 patients with primary Raynaud's, 12 with secondary Raynaud's associated with scleroderma and 10 controls, and eight patients with scleroderma and nine controls)[8, 9] finger capillary blood flow was not significantly affected during moderate systemic cooling in controls but finger capillary blood flow was slightly reduced in primary Raynaud's and almost abolished in secondary Raynaud's patients.

Vascular abnormalities lead to the balance between vasoconstriction and vasodilator to be tipped in favor of vasoconstriction. There may be a mismatch between the endothelium-derived vasoconstrictors such as endothelin-1 and vasodilators such as nitrous oxide and prostacyclin. Intravascular abnormalities promoting vasoconstriction may include platelet activation with increased thromboxane. There may be defective fibrinolysis and white blood cell activation. Red blood cells may have reduced deformability and increased viscosity may occur. Ultimately, ischemic reperfusion injury may lead to additional oxidative stress. Neural abnormalities including impaired vasodilation due to calcitonin gene related peptide deficiency also contribute. Arteriovenous anastomese are controlled by sympathetic adrenergic nerve activity and if increased stress occurs, there is increased vasospasm.

Sympathetic adrenergic vasoconstriction in those with Raynaud's is also targeted to proximal arteries and this disruption of capillary blood flow is most profound in those with secondary Raynaud's. Increased vasoconstriction mediated by activation of the alpha2-adrenoreceptors in the thermoregulatory process also occurs. Smooth muscle from cutaneous vessels is predominately innervated via the alpha2 adrenoreceptors. Cooling induces activation of Rho/Rho kinase signaling pathway which causes alpha-2c adrenoreceptors stored in the Golgi apparatus to translocate to the cell surface and causes increased sensitivity to calcium of contractile proteins.[10] Other factors such as cigarette smoking, genetic factors, and hormonal influence are also significant. Several studies have shown that during the immediate pre-ovulatory period, healthy controls demonstrated digital vascular reactivity similar to that of patients with Raynaud's.

## Diagnostic Evaluation

Prompt recognition of Raynaud's by clinical history is key and referral to a rheumatologist is encouraged. A detailed history and physical exam along with use of nail fold capillaroscopy will guide the rheumatologist in their laboratory evaluation. Typically work-up will include complete blood count, comprehensive metabolic panel, muscle enzymes, rheumatoid factor, anti-cyclic citrullinated peptide, thyroid studies, hepatitis screening, anti-neutrophil cytoplasmic antibodies, anti-phospholipid antibodies. Most important would be investigation for antibodies associated with connective tissue diseases as Raynaud's is often the first presenting sign or symptom of several of these diseases such as scleroderma, mixed connective tissue disease, dermatomyositis, or lupus. Labs including anti-nuclear antibody by immunofluorescence (ANA), anti-double stranded DNA, anti-SSA, anti-SSB, anti-Smith, anti-ribonucleoprotein, anti-Scl-70, anti-centromere, anti-fibrillarin, anti-Pm-Scl, anti-RNA polymerase III, and possibly a myositis profile may be obtained. Further investigations may require serum protein electrophoresis, cryoglobulins, cold agglutinins, venous/arterial dopplers, or angiography depending on the clinical scenario.

## Therapy

Patient education is the primary therapy recommended. Avoiding sudden cold and rapid changes in temperatures should be emphasized. Keeping the hands and feet warm as well as keeping the total body warm is important. Patients should be counseled to avoid tobacco and caffeine which may exacerbate symptoms. Avoidance of sympathomimetic drugs such as decongestants, amphetamines, and methylphenidate will help control symptoms. If Raynaud's is thought to be vibration induced, discontinuation of vibratory tools such as jackhammers would be of benefit. As a better understanding of the pathophysiology arises, medical therapies will likely also improve. Currently, calcium channel blockers are the most common and practical treatment. These vasodilators have a direct effect on vascular smooth muscle and inhibit platelet aggregation. A meta-analysis of 18 randomized placebo controlled and double-blinded trials were evaluated and showed use was associated with a 33% reduction in severity and an average decrease of 2.8-5.0 attacks over a one-week period.[11] A Cochrane review of calcium channel blockers for primary Raynaud's also showed a decrease in frequency of attacks by around 1.7 attacks per person per

week.[12] Nifedipine is the most commonly used and most studied and can be dosed usually at 30-60mg per day, if the blood pressure permits its use. Other calcium channel blockers shown to help include nisoldipine, amlodipine, felodipine, and isradipine. Verapamil has not been shown to be effective. There also remains a concern that short-acting dihydropyridines may increase cardiovascular risk so these should be used with caution. If a patient is intolerant to calcium channel blockers, losartan, an angiotension II receptor blocker, may be considered.

A randomized, parallel-group, controlled trial demonstrated a reduction in the severity of Raynaud's episodes and decreased episode frequency with use of losartan 50mg daily.[13] Intravenous iloprost, a prostaglandin analogue, is a potent vasodilator and inhibitor of platelet aggregation, and remains a key medication for management of scleroderma patients with severe digital ulcerations. IV iloprost appears effective at decreasing frequency and severity of attacks. It also may prevent or heal digital ulcers with the effect prolonged after the intravenous infusion is given. [14] Oral prostaglandins show mixed results and more studies are needed to determine their efficacy. Endothelin 1 is the most potent endogenous vasoconstrictor. There are endothelin A and B receptors on vascular smooth muscle. In addition there are endothelin A receptors on cardiac myocytes and endothelin B receptors on endothelial cells. Bosentan is a nonselective endothelin A and B receptor antagonist. In a randomized, double-blind, placebo-controlled study of 188 patients with scleroderma with at least one active digital ulcer at baseline, treatment of bosentan reduced the number of new digital ulcers by 30% compared to placebo but did not increase the healing rate of existing ulcers.[15] Phosphodiesterase inhibitors prevent the degradation of cGMP which mediates nitric oxide synthesis and release. Nitric oxide serves as a potent vasodilator, inhibitor of platelet activation, and inhibitor of vascular smooth muscle proliferation. Studies of sildenafil, vardenafil, and tadalafil have all shown benefit on Raynaud's symptoms [16 17 18] with regards to decreased frequency of attacks and symptoms, although many studies are limited in number of patients and limited in follow-up time of less than 8 weeks. Topical nitrates can induce local vasodilation but have not been shown to be effective in limited studies and side effects of headaches and tachyphylaxis limit their use.

Statins have direct vasculoprotective effects as they increase endothelial nitric oxide synthase and nitric oxide production, decrease endothelin-1 expression, and promote microvascular growth but there is insufficient evidence for statins to be recommended as standard therapy for Raynaud's; however, a study of use of atorvastatin at 40mg per day for 4 months did show a reduction in the overall number of new digital ulcers in scleroderma patients. [19] Small studies of gingko biloba and St. John's Wort showed no clinical benefit over placebo in Raynaud's. Botulinum toxin A is currently under investigation as a treatment for Raynaud's as it may potentially have an effect on inhibiting sympathetic vasoconstriction.

## Conclusion

Raynaud's syndrome is a relatively common phenomenon and patients should be referred promptly to a rheumatologist to assist with differentiation between primary and secondary Raynaud's. The extent of the work-up will be guided by a detailed history and physical exam but is important to pursue as Raynaud's is often the earliest presentation of an underlying connective tissue disease. Patient education is a crucial part of the treatment. As the pathophysiology becomes better understood, treatments will also likely improve, but current therapies do exist to prevent new ulcer formation and to improve symptoms.

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## Disclosure

None reported. **MM**

# Inflammatory Myopathies

*by Rama Bandlamudi Atluri, MD*

**This article summarizes the clinical, histochemical, and immunological features as well as the treatment options of the inflammatory myopathies.**



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## Abstract

**Idiopathic inflammatory myopathies are relatively rare diseases. Polymyositis and dermatomyositis are more common in women than men (2:1 ratio), while inclusion body myositis is twice as common in men. Inflammatory myopathies are a heterogeneous group of chronic systemic autoimmune diseases with an annual incidence of two to five cases per million, characterized by muscle inflammation and progressive muscle weakness. There are three major diseases which includes Dermatomyositis (DM) including a distinct juvenile subtype (JDM), Polymyositis (PM), and Inclusion Body Myositis. DM is a compliment mediated microangiopathy affecting skin and muscle. PM and IBM are T-cell mediated disorders, where CD8 positive cytotoxic T cells invade muscle fibers expressing MHC class I antigens, this leading to fiber necrosis. In IBM, vacuolar formation with amyloid deposits are also present. This article summarizes the clinical, histochemical and immunological features as well as the treatment options of the inflammatory myopathies.**

## Dermatomyositis

Dermatomyositis (DM) is a multisystem autoimmune disease that affects children and adults, characterized clinically by progressive symmetrical proximal muscle weakness and specific skin manifestations, including Gottron's papules, heliotrope rash, and macular erythema.[1] The skin manifestations may precede myositis onset by months or years and can be worsened by sun exposure. Major differences between juvenile and adult DM include the presence of subcutaneous calcinosis affecting the elbows and knees with or without ulceration in Juvenile DM.[2] Other manifestations including, arthralgia, dysphagia, Raynaud's phenomenon, and pulmonary symptoms.[9] About 20 to 25% of the times it can be associated with an underlying malignancy, in particular lung, ovarian or gastrointestinal tract, as well as with other connective tissue diseases.

### *Immunopathogenesis*

DM is a humorally mediated autoimmune disorder. Complement dependent attack leads to destruction of capillaries in muscle and other tissues. The etiology is not well understood, it has been suggested that genetically susceptible individuals probably develop myositis in response to particular environmental stimuli.

Characteristic of DM is persisting damage to the vascular endothelium of endomysial capillaries and lesser extent of larger blood vessels. Membrane attack complex deposits, are noted on small arterioles and capillaries supplying the muscle fibers (compliment mediated).[2] The result is a marked reduction in the number of capillaries fallowed by dilation of remaining capillaries. The endothelial cells become swollen and necrotic, and develop tubuloreticular inclusions and microvacuoles. These changes results in perivascular inflammation, muscle ischemia and the characteristic perifascicular atrophy.

## Polymyositis

The Polymyositis (PM) is an immune mediated syndrome secondary to defective cellular immunity that is most commonly associated with other systemic autoimmune diseases. PM rarely effects people under the age of 20, with the peak onset between the ages of 30 and 60. The proximal muscle weakness develops as a sub-acute myopathy, usually over weeks to months. Patients present with neck flexor and symmetric proximal upper and lower extremity weakness that develops slowly.[2] Distal muscle may become involved but to a lesser degree. Dysphagia occurs in a third of patients due to oropharyngeal and esophageal involvement. Usually extraocular muscles are spared. Weakness of neck flexors also occurs.

Extra muscular manifestations of polymyositis:

- Constitutional symptoms, such as fever and fatigue
- Articular symptoms of polymyositis: rheumatoid like arthropathy
- Severe interstitial lung disease (ILD)
- Cardiac manifestations: are unusual, rhythm disturbances, conduction defects, congestive heart failure, pericarditis, pulmonary hypertension and myocarditis can occur
- Cutaneous manifestations: mechanic's hands

### *Pathogenesis*

Polymyositis is characterized by T-cell mediated injury. Class I and II MHC upregulation is an early and consistent finding in the skeletal muscle of PM patients, the interaction of muscle with infiltrating CD8+ and CD4+ T cells. CD138-positive plasma cells are also abundant in endomysial areas and are probably the main source of autoantibodies in PM muscle.[2] IFN-γ transcript expression has been shown up-regulated in PM muscle compared to other IIM and also control muscle, emphasizing the involvement of IFN-γ is also involved in the induction of MHC class II molecules present on muscle fibers in PM muscle.[7] IFN-γ is also involved in the synthesis of important chemotactic γ cytokine that govern leukocyte migration from blood to sites of inflammation (CCL2, CXCL9 and CXCL10) and sustain the active invasion of nonnecrotic myofibers by inflammatory cells. The high levels of IFN-γ, as well as of IL-4 and IL-17, present in PM muscle, suggest involvement of activated CD4+T cells in the pathophysiology of this disorder.

## Clinical Presentation of Polymyositis and Dermatomyositis

Muscle pain and tenderness are present in half of the patients. They can have arthralgia, fatigue, anorexia, weight loss, and fever. Pulmonary and cardiac manifestations may occur at any time during the course of the disease. Interstitial pneumonitis may cause dyspnea, cough, hypoxemia, and fatal respiratory failure. Aspiration pneumonia can complicate the disease course due to esophageal dysmotility. Heart block, supraventricular arrhythmia or cardiomyopathy may develop, may cause syncope, palpitations or congestive heart failure. In dermatomyositis, besides myositis that is similar to polymyositis, plus cutaneous manifestations are seen. Rash is often the presenting compliant. A variety of skin changes can be seen. The pathognomonic skin manifestation is Gottron's papules. These are symmetric, lacy, and pink to violaceous raised or macular areas typically found on the dorsal aspect of interphalangeal joints, elbows, patellae and medial malleoli. Other changes include heliotrope (violaceous) discoloration of the eyelids, often with associated periorbital edema, macular erythema of the posterior shoulders and neck (shawl-sign), anterior neck and upper chest (V-sign), face and forehead. Periungual telangiectasias, dystrophic cuticles and nail fold capillary changes are frequently seen. Darkened or dirty-appearing horizontal lines may be noted across the lateral and palmar aspects of the fingers. These changes are termed mechanic's hands. Cutaneous vasculitis can occur with livedo reticularis, digital infarcts or palpable, white centered petechia. Periungual erythema, cuticular overgrowth, and dilated capillary loops seen in nail folds. See Figures 1 and 2.

## Laboratory Testing

Serologic testing can indicate muscle damage, includes elevations in creatinine phosphokinase (CPK) aldolase, lactate dehydrogenase (LDH, and liver function enzymes.[6] Specific autoantibody testing is helpful to determine prognosis and rule out associated conditions. Anti Jo-1 antibodies are found in 15-20% of patients, associated with ILD, anti- Mi-2 is marker for DM and associated with good response to steroid treatment with good prognosis. Anti-SRP is specific for PM and associated with treatment-resistant myopathy. Antibodies to transcription intermediary factor 1γ/α (TIF1γ/α, ρ 155/140) are frequently found in DM associated with malignancy while anti-melanoma differentiation-associated gene 5 (MDA5; CADM140) are associated with clinically amyopathic DM (CADM) complicated by rapidly progressive ILD.



**Figure 1**
Dilated capillary loops and cuticular overgrowth in the nail beds



**Figure 2**
Gottron papules: erythematous lichenoid popular scaly rash over the extensor surface of the hands and fingers.

## Electro-Diagnostic Studies

The electromyogram (EMG) is an electrical study of the nerves and muscles that plays an important role in confirming the presence, duration and severity of a myopathy. In PM increased insertional activity, fibrillations and sharp positive waves, spontaneous, bizarre high frequency discharges and polyphasic motor unit potentials of low amplitude and short duration seen in 40% of the patients. EMG can be normal in mild myopathies, therefore normal EMG does not exclude the presence of a myopathy.

## Magnetic Resonance Imaging (MRI) Scanning

MRI of the muscle can be helpful to direct muscle biopsy.[8] Areas of inflamed muscle demonstrate increased signal on T2-weighted images with fat suppression (STIR) images denoting areas of inflammation/edema. In chronic cases of myositis MRI can show fatty degeneration on T1 weighted images. Muscle biopsies from sites which are affected by MRI have a higher intensity of inflammatory infiltrates as compared to those obtained from nonaffected MRI locations, thus the performance of both MRI and biopsy has a superior diagnostic yield.

## Muscle Biopsy

Histopathologic examination is very helpful in determining the specific type of muscle disease. Muscle fibers are found to be in varied stages of necrosis and regeneration. The inflammatory cell infiltrate is predominantly focal and endomysial. T-lymphocytes, especially T8+ cytotoxic cells accompanied by a smaller number of macrophages are found surrounding and invading initially non necrotic fibers. Destroyed fibers are replaced by fibrous connective tissue and fat. In dermatomyositis perivascular distribution of inflammatory cells, composed of higher percentages of B lymphocytes and helper T4+ lymphocytes. Perifascicular atrophy also seen.

## Treatment

Oral and intravenous steroids are most commonly used, regimens of daily prednisone at a dose of 1.5 mg/kg per day or intravenous methylprednisolone at 500 to 1000 mg for three to five days are recommended depends on severity of the disease.[1] Methotrexate, azathioprine, mycophenolate mofetil are help full for rash, muscle disease and ILD as steroid sparing agents, Hydroxychloroquine is help full for the rash. Cyclophosphamide is helpful in refractory cases. Intravenous immune globulin (IVIG), (2 g/kg over five days initially and followed by a monthly three-day courses is effective. Tacrolimus is effective in resistant PM. Cyclosporine has also been used. Rituximab has recently been shown to be effective DM and PM patients with myositis specific antibodies.

Repository corticotropin injection (H.P.Acthar gel): this is FDA approved for treatment with DM/PM (80 USP units subcutaneously twice a week) for three months then decrease the dose.

## Inclusion Body Myositis

Inclusion Body Myositis (IBM) is a subset of inflammatory myopathy, most commonly seen in an older population, over 50 years, and is more common in men. It is a gradual onset myositis and it may take several months to years from the onset of symptoms, till the diagnosis is made. It exists in sporadic and familial farm. IBM usually affects proximal as well as distal muscles, the most frequent symptom is frequent falls. Muscle atrophy and swallowing difficulty are also seen in IBM. It is associated with changes identical to polymyositis but also demonstrates lined vacuoles and deposits of beta-amyloid and ubiquitin.[2] It is associated with other connective tissue

diseases in about 15% of patients. About 30% of patients can have myositis specific abs and serum CK levels are only slightly elevated in most patients. EMG may show neurogenic or mixed neurogenic and myopathic changes.

### *Pathogenesis*

IBM is a multifactorial disease with autoimmune and degenerative features. Histologic changes include necrosis and inflammation, ragged red fibers and angulated atrophic fibers may be seen. The characteristic change is the presence of intracellular lined vacuoles. Electronic microscopy reveals either intracytoplasmic or intranuclear tubular or filamentous inclusions.

### *Treatment*

Patients respond poorly to immunosuppressive therapy, and the course is typically progressive. Rarely patients will respond to prednisone alone or in combination with other immunosuppressive medications like methotrexate and azathioprine, so they should be treated for at least four to six months.

## The Antisynthetase Syndrome (AS)

The antisynthetase syndrome is a triad of polymyositis, diffuse interstitial lung disease (ILD), and serum autoantibodies to aminoacyl transfer RNA synthetase. Anti jo-1anibody is the most common antibody found. ILD is the clinical hall mark of AS. Usually, the myositis is less severe than in DM and PM without anti AS antibodies. At onset of disease, respiratory symptoms are present in 40-60% of patients, they may also present with constitutional symptoms such as fever, loss of appetite, and weight loss. Joint pain, arthritis, tenosynovitis and Raynaud's phenomenon.[3] Most reports indicate that the frequency of ILD in the AS is in the range of 70-95%. ILD seems to be highest in patients with antibodies to PL-12.

All the patients with AS in addition to evaluation for ILD should be evaluated for pulmonary hypertension (ECHO), and barium esophageal X-ray to assess for esophageal dysmotility

### *Treatment*

In acute and subacute farms corticosteroids are helpful, either high dose IV methylprednisolone (500-1000 mg/day for three days), or oral corticosteroids (1mg/kg/day). In moderate to mild cases a combination of oral glucocorticoids and either cyclophosphamide, azathioprine, or methotrexate may be recommended. In some retrospective case series, they recommend a combination of oral corticosteroids, cyclophosphamide, and the anti-CD-20 monoclonal antibody rituximab as induction therapy in AS are recommended. Cyclosporine A, mycophenolate mofetil and tacrolimus are also showed efficacy.

### *Statin-Induced Necrotizing Autoimmune Myopathy*

Necrotizing autoimmune myopathy (NAM) is relatively newly recognized subgroup of idiopathic inflammatory myopathies. Patients may present with a subacute severe symmetrical proximal myopathy, associated with a markedly elevated creatine kinase level. It can be associated with an antibody against the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) protein, which is upregulated in regenerating fibers [4]. This may suggest that NAM is an antibody-mediated disease, and may explain the continuing progression of disease despite cessation of the statin.

NAM can be distinguished from the other inflammatory infiltrates with macrophages rather than T-cells being the effector cells.[5] Immunostaining of muscle biopsies shows macrophages around necrotic fibers without many lymphocytes. An antibody dependent complement-mediated lysis may be responsible, with macrophages as seen on muscle biopsies.

Patients with statin-induced myopathy can have symptoms years after starting or even stopping the treatment. They can have persistence or progression of symptoms despite stopping statins. Treatment is oral corticosteroids 1mg/kg/day and depends on severity of symptoms. Steroid sparing agents, such as methotrexate, azathioprine, mycophenolate, and IVIG can be used as an adjunct. Rituximab was also shown to be effective when used with corticosteroids.

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## Disclosure

None reported.

**MM**

# Evaluating the Limping Child: A Rheumatology Perspective

*by Reema Syed, MD*

**Taking a detailed history and completing a thorough evaluation will help hone in on the underlying cause. This article will review important causes of limp from the rheumatologist's viewpoint.**



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## Abstract

**Children often present to health care providers for evaluation of limp. Having the knowledge of the different causes of leg pains both in the acute and chronic settings will help in diagnosis, treatment, and referrals to subspecialists in a timely manner. Taking a detailed history and completing a thorough evaluation will help hone in on the underlying cause. This article will review important causes of limp from the rheumatologist's viewpoint.**

## Introduction

A child may present to a primary care provider with a limp due to acute more urgent issues like infections or for more chronic issues like juvenile idiopathic arthritis or other rheumatologic issues. Picking up key information on history and a detailed examination will often lead a provider closer to the correct diagnosis.

## Clinical Evaluation

### *History*

Obtaining a detailed history regarding and surrounding the child's presenting symptoms will help narrow the differential diagnosis. Acuity of onset, duration of symptoms, preceding injury or infections, associated symptoms such as fevers, rashes, weight loss, fatigue are important clues to the underlying diagnosis. Inquiring about recent travel will help with infectious causes. Associated pain versus painless limp raises different possibilities.

### *Examination*

Assessing a child's gait is crucial in completing an evaluation for lower extremity complaints. Is the child unable to bear weight or is the child holding the affected joint in a fixed position are important questions to address and are signs of more serious issues. If the child appears toxic or has high fevers infectious etiologies need to be excluded.

An antalgic gait signifies pathology in the hip, knee or ankle. A child with antalgic gait will take a shorter stance on the affected limb to avoid bearing weight on the diseased painful joint. A circumduction motion of the hip is also a clue of a painful joint aggravated by motion. Non-antalgic gait include toe walking for instance in leg length discrepancy or due to tight heal cords. Trendelenburg gait is another form of non-antalgic gait seen with weak abductor muscles.

The exam should not be limited to the affected joint but rather include the entire musculoskeletal system looking for tenderness, swelling, warmth, erythema, ligament laxity, and restriction in range of motion. The back and spine should also be examined as well as the skin, which may provide clues.

## Causes of Acute Limp

### *Septic arthritis*

Septic arthritis is a medical emergency, which if not addressed promptly may lead to damage within one to two days.[1] The most commonly affected joint is the knee but other joints including the hips and other large more than small joints may be involved. The child is usually febrile with inability or refusal to ambulate with a painful limp if child does ambulate. The involved joint is warm, swollen, and erythematous, with limited range of motion. In case of the hip no swelling is found on exam and the child holds the joint in a flexed, abducted, and externally rotated position. The most common causative organism is *Staphylococcus Aureus* but may be different strains of streptococcus in neonates and infant, *salmonella* in sickle cell patients, and *Neisseria gonorrhea* in sexually active adolescents.[2] The affected joint fluid should be aspirated which will reveal elevated WBC > 50,000 and cultures will be positive in 70% of individuals. Blood cultures will be positive in 50% of patients. Infected joints will need to be irrigated to allow for better healing. The hip joint always needs to be opened and surgically drained to prevent joint damage. Intravenous antibiotics should be started promptly followed by oral antibiotics for at least three weeks is needed for complete recovery.



A child may present to a primary care provider with a limp due to acute more urgent issues like infections or for more chronic issues like juvenile idiopathic arthritis or other rheumatologic issues. Picking up key information on history and a detailed examination will often lead a provider closer to the correct diagnosis.

## Osteomyelitis

Child will present acutely with fevers, localized pain, limping or refusal to ambulate.[3] The most commonly involved bone is the femur and the most common causative organism is *Staphylococcus aureus* either via blood or direct spread from adjacent infected tissue. There may be soft tissue swelling, local tenderness on palpation, and pain with resistance on range of motion of the affected joint. Blood cultures are positive in 60% of cases and bone cultures are positive in 80%. There usually is a delay in changes on plain xrays by a week or more such as soft tissue swelling, subperiosteal changes, and bone destruction.[4] Thus if the suspicion is high, bone scan or MRI, which is as sensitive but more specific than a bone scan, should be performed. Treatment should be started promptly with intravenous antibiotics followed by four to six weeks of oral antibiotics.

### *Toxic Synovitis*

Toxic synovitis is self-limited benign inflammation of the hip following a recent upper respiratory infection within the last few weeks up to four months. Child will present acutely with a painful limp, which usually resolves over seven to ten days.[5] Boys between the ages of three and ten years are affected more than girls. The child does not appear toxic or as ill as in septic arthritis or osteomyelitis. Low-grade fevers may be noted and child will hold the affected hip in a flexed and externally rotated position. To help differentiate septic arthritis from toxic synovitis Kocher et al. determined four clinical predictors, if present, are more in favor of septic arthritis: fevers more than 101.3°F, blood white cell count greater than 12,000/$\mu$L, erythrocyte sedimentation rate (ESR) more than 40mm/hour, and inability to bear weight. Caird et al. added c-reactive protein (CRP) more than 2.5mg/dL to the criteria. Treatment is symptomatic with NSAIDs and most children recover in seven days with or without treatment though NSAIDs may shorten treatment. Seventeen percent of children may have recurrence out of which 10% may go on to develop inflammatory arthritis especially seronegative spondyloarthropathy.[6] Synovial fluid will reveal WBC counts between 5000 to 15000/$\mu$L and negative cultures. The serum WBC, ESR, and CRP are mildly elevated.

### *Trauma*

Limping is a common manifestation of ligament strains, muscle strains, contusions, and fractures and should be kept in mind whenever a child presents with a limp.[7,8] Apophysitis usually presents subacutely or is chronic but avulsion fractures may present acutely. Runners are especially prone to avulsion fracture of the anterior superior iliac spine at the insertion of the Sartorius muscle.

Compartment syndrome is one complication of fractures and may lead to severe swelling and diminished distal blood flow and should be recognized.

Traumas are addressed more often by orthopods thus beyond the scope of this paper.

## Chronic Causes of Limp

### *Juvenile Idiopathic Arthritis*

Juvenile Idiopathic Arthritis (JIA) is noninfectious joint swelling, which persists in a child 16 years or younger for more than six weeks. The prevalence of JIA in the U.S. ranges from 1.6 to 86.1 per 100,000 persons.[9] It is the most common rheumatic illness in childhood. Underlying etiology is multifactorial occurring in genetically susceptible host in the opportune environment. There are 17 loci found to be associated with JIA risk. The concordance rate in monozygotic twins is between 25-40%. Many cytokines are elevated in JIA including Tumor Necrosis Factor-alpha, Interleukin-1, Interleukin-6, which cause activation and proliferation of many inflammatory cells and adhesion molecules.

JIA is subclassifed based on the International League of Associations for Rheumatology (ILAR) into systemic onset (SoJIA), oligoarthritis with involvement of four or less joints, polyarthritis rheumatoid factor negative, polyarthritis rheumatoid factor positive, psoriatic arthritis, enthesitis related arthritis, and other arthritis.[10] The oligoarthritis is subclassifed further into persistent if the number of joint counts after six months of disease onset remain less than five or extended if five or more joints become involved.

SoJIA presents with quotidian fevers with daily spikes up to 40° and evanescent salmon colored rash which becomes prominent with fevers. Patient has polyarthralgia or arthritis. Most of these children appear very ill with systemic manifestation such as lymphadenopathy, hepatosplenomegaly, pericarditis, or serositis. Infections and malignancy must be ruled out. Though limp may occur it is not as prominent a feature of SoJIA as are the systemic symptoms and thus this subtype of JIA will not be discussed further.

### *Oligoarticular JIA*

Oligoarticular JIA is the most common form of chronic inflammatory arthritis in childhood making up 40% of all JIA. Four or less joints are involved at onset, which may persist after six months of disease or extend to involve five or more joints. Oligo-JIA is mainly seen in younger kids two to four years of age and is three times more prevalent in girls than boys. The most commonly involved joint is the knee and the most common presentation is joint swelling and limp.[11, 12] The child may have morning stiffness manifested as refusal to walk in the morning or slow awkward gait. Examination of the affected joint(s) reveals swelling and may be warm with pain on range of motion. Unlike in SoJIA labs overall are normal with usually normal blood cell counts, inflammatory markers (ESR, CRP), and ferritin. ANA is positive in 70-80% of oligo-JIA patients and increases the risk of silent uveitis. The rheumatoid factor (RF) and anti-cyclic citrullinated peptides (anti-CCP antibodies) are mostly negative in oligoarticular JIA.

## Complications Seen in Oligoarticular JIA

### *Uveitis*

Uveitis specifically involving the anterior chamber is seen in 45% of oligo-JIA patients. Risk factors to developing uveitis besides the positive ANA include earlier onset of disease < four years of age and female gender.[13] The course of joint disease does not correlate with eye disease. Five percent of patients present with eye disease prior to developing joint disease, which is linked with poorer prognosis. If a child is diagnosed with JIA especially oligoarticular JIA they must be referred to ophthalmology for evaluation for uveitis.[14] In patients with positive ANA follow-ups with ophthalmology should be every three months for three to four years then spaced out to every six months for another three years then annually. Those with a negative ANA need to be followed by ophthalmology every six months. Untreated uveitis may lead to visual loss, band keratopathy, posterior synechiae, and formation of cataracts, glaucoma, and abnormal intraocular pressures.

### *Leg-Length Discrepancy*

Oligoarticular JIA when left untreated or if there is a delay in treatment may lead to leg-length discrepancy since the large joints of the lower extremities are mostly involved. Due to inflammation, the ossification centers mature prematurely causing premature fusion of the growth plate and growth arrest.[15]

## Treatment of Oligo-JIA

American College of Rheumatology treatment guidelines were originally made in 2011 which were further updated in 2013.[16, 17] Patients with oligo-JIA are started on nonsteroidal anti-inflammatory drugs (NSAIDs) on a regimented schedule. Most children respond very well to NSAIDs. Some patients respond partially and other develop extended oligoarthritis with five or more involved joints and require disease modifying anti-rheumatic drugs (DMARDs). First line DMARDs is methotrexate, which is overall very well tolerated. A few patients continue to have active disease despite use of NSAIDs and DMARDs and require biologic DMARDs specifically anti-TNF agents: etanercept, adalimumab, infliximab, anti-IL 6 agent: tocilizumab, or CTLA-4 fusion protein: abatacept. In case of monoarticular arthritis not responding to NSAIDs, a corticosteroid injection to the affected joint may be very beneficial.

### *Polyarthritis JIA*

Polyarthritis RF positive patients present with symmetric small and large joint involvement. This subclass

appears in older adolescent females and appears similar to adult rheumatoid arthritis.[18]

Polyarthritis RF negative patients have similar joint involvement as oligoarthritis patients except for the number of joints involved at disease onset is more than five. This is the second most prevalent form of JIA and similar to oligoarthritis ANA positive patients are at risk for silent uveitis especially if the ANA is positive.[18] These patients present with joint pains, swelling, stiffness lasting for more than one hour, and with limp if lower extremity joints are involved.

For treatment corticosteroids are very often needed initially in polyarthritis patients since these patients are in a lot of pain with restriction or difficulty in activities of daily living. Most patients will need DMARDs and many require biologic agents since disease persists despite use of NSAIDs and DMARDs.

### *Lyme Arthritis*

Arthritis in Lyme disease is the second most common manifestation after erythema migrans and occurs in two third of patients. It is caused by borrelia burgdorferi and transmitted by tick bites. It is most prevalent in northeastern states from Northeastern Virginia to Maine; Midwestern states mainly Wisconsin and Minnesota, and Northern California. School age children are the most affected age group. Most patient do not recall a history a tick bite. Arthralgia develops in the early phase of disease; the onset of arthritis may be delayed by months to years.[19] Initially the arthritis is episodic but over time become more prolonged and recurrent. Diagnosis is made by obtaining lyme cultures or PCR in the blood, synovial fluid, or synovial tissue. Western blot assays may show 2 IgM or 5 IgG bands which is consistent with lyme disease. It should be kept in mind that IgG titers may remain positive for years after adequate treatment and cannot be used to assess treatment response or failure.

The recommended treatment is either intravenous ceftriaxone for 14 days or oral amoxicillin or doxycycline for four weeks.[3] NSAIDs may be used for symptomatic relief of pain and swelling.

### *Legg-Calve-Perthes*

Legg-Calve_Perthes (LCP) disease in another cause of chronic limp due to idiopathic avascular necrosis of the femoral head epiphysis. It occurs in five to seven-year olds and affects boys four times more than girls. Bilateral hip involvement is seen only in 10% of cases occurring in an asynchronous fashion. LCP tends to be self-limited as the initial interruption of blood supply in the lateral epiphyseal vessels, which supplies the femoral head, is eventually restored. The child presents with painful limp insidious in onset and on examination has limited hip range of motion. There are no preceding infections as seen in toxic synovitis, or fevers and/or rashes as may be seen in SoJIA or malignancy. Risk factors for worse outcome include older age of onset, more advanced changes at initial presentation, and hip deformities after remodeling.

Initial stages of LCP as seen on imaging reveal a dense and sclerosed femoral head epiphysis. A subchondral fracture line "crescent line" may be seen which demarcates the extent of the infarction.[4] Later in this initial stage the femoral epiphysis begins to lose height. The second stage is fragmentation phase, when fissures perpendicular to the articular surface appear within the dense physis. During this phase the articular cartilage hypertrophies and the femoral head may be displaced outside the acetabulum. The next phase is the regenerative phase during which new bone forms and healing begins, but if the femoral head has been displaced then there will be chronic deformation. During this phase there is neovascularization or recannulation of the existing vessels, which may result in early epiphyseal closure. The final stage is the healed stage. Most hips heal without sequelae or residual deformities. Factors for poor prognosis and early osteoarthritis include enlarged femoral head, short femoral neck, and significantly deformed femoral head. The factors contributing to poor prognosis include obesity, progressive loss of hip motion, adduction contracture, and longer duration between disease onset and to healing phase.

Treatment is initially symptomatic with NSAIDs to control pain, joint protection by limiting activities, and physical therapy. These patients need to be referred to orthopedic surgeons for further assessment and long-term management.

### *Slipped Capital Femoral Epiphysis (SCFE)*

SCFE is another cause of chronic limp and is due to the displacement of capital femoral epiphysis from the metaphysis of the femur due to abnormality in the physis. This is an orthopedic emergency. SCFE occurs typically in an obese older child or adolescent 10-14 years of age.[20] Boys are affected more than girls in SCFE. It is divided into stable and unstable. In stable SCFE, which is the more common presentation occurring in 90% of cases, a child is able to bear weight and has better prognosis in the long run. Unstable SCFE, when the child is unable to bear weight, has much worse outcome because of potential severe avascular necrosis. On examination the child has an antalgic gait with out-toeing and limited internal rotation of the hip. They may complain of hip, thigh, or knee pain. A third of patients will have bilateral SCFE. This disease is associated

with endocrinopathies such as hypothyroidism or growth hormone deficiency. Radiographic imaging is diagnostic and if found, patient should be immediately admitted to the hospital for orthopedic evaluation and surgical management. They should be made non-weight bearing immediately until after surgical intervention.

### *Osgood Schlatter Disease (OSD)*

OSD is apophysitis of the tibial tuberosity and may cause limping but more pain at the tibial tuberosities that is exacerbated by activities. OSD occurs more often in older boys 9-14 years of age but may occur in girls at a younger age.[4] On examination child will have point tenderness at the tibial tubercles with possibly some soft tissue swelling or bony prominence of the tubercle. Treatment is symptomatic with NSAIDs, restriction of activities, and icing at area. Symptoms resolve when the tibial tubercle closes around age 15 years.

### *Benign Joint Hypermobility Syndrome (BJHS)*

BJHS presents mainly with joint pains and some limp. The affected child may have lower extremity pain especially later afternoon or at the end of the day. Many patients will have nocturnal pain, which awakens them from sleep, which is relieved with rubbing, heat, and NSAIDs. One in five girls and one in ten boys are hypermobile. Three-quarters of these hypermobile children have musculoskeletal pain. Increased range of motion of the knees or ankles due to ligament laxity may lead to repeated microtrauma to tendons and early osteoarthritis.[21] These patients tend to be clumsy due to impaired proprioception. Recurrent joint subluxation, papyraceous scars, loose skin, lens abnormality, and increased capillary fragility should raise the suspicion for Ehlers Danlos or Marfan's syndrome. Patients with trisomy 21 also tend to be hypermobile in most joints leading to premature osteoarthritis and ligamentous injuries. Treatment is based on muscle strengthening for joint protection. Isometric and strengthening exercises, proprioception training, and avoiding over stretching are key to protecting the joints and minimizing pain. Water therapy is very beneficial for strengthening.

## Summary

Children may present acutely or chronically with a limp. Acute infectious causes such as septic arthritis and osteomyelitis must be treated immediately to preserve joint anatomy and function. Oligoarticular JIA may present with limp; delay in diagnosis may lead to significant morbidity with leg length discrepancy or silent uveitis.

SCFE is an orthopedic emergency, which required immediate surgical intervention. On the other hand LCP disease is usually a self-limited disease requiring symptomatic treatment. A good history and examination will help narrow down the differential diagnosis.

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## Disclosure

None reported. **MM**

# Undifferentiated Connective Tissue Disease, Mixed Connective Tissue Disease, and Overlap Syndromes in Rheumatology

*by Peri Hickman Pepmueller, MD*

**An average of 30% of undifferentiated connective tissue disease eventually develop a defined CTD, while the majority remain active but with undifferentiated disease. Fortunately, in patients who remained undifferentiated, there tends to be absence of major organ involvement.**



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## Abstract

**Autoimmune diseases often have overlapping symptoms and laboratory somewhat unfamiliar to the non-rheumatologist. Characteristic signs, symptoms, and autoantibodies define specific connective tissue diseases. Some patients have some characteristic symptoms, but cannot be definitively classified. Still other patients meet criteria for more than one specific connective tissue disease. These patients can be confusing with regard to diagnosis and prognosis. Clarification of each patient's condition can lead to improved patient care.**

## Introduction

Autoimmune diseases are complex and in general, relatively rare. Characteristic signs, symptoms, and autoantibodies define specific connective tissue diseases. Some patients meet criteria for more than one defined connective tissue disease (CTD), while others have several symptoms characteristic of autoimmune diseases yet cannot be definitively classified. This variability can lead to confusion, especially to the non-rheumatologist. This article will help remove confusion regarding the diagnoses mixed connective tissue disease (MCTD), overlap syndromes, and undifferentiated connective tissue disease (UCTD), as well as in enhance understanding of these conditions.

Currently, there are criteria for classification for five defined autoimmune connective tissue diseases. These include: Systemic lupus erythematosus (SLE), scleroderma, myositis, rheumatoid arthritis (RA), and Sjogren's syndrome. All five are variable in presentation, but generally over time, the diagnosis of a defined CTD is readily apparent. Some patients, however, may have features characteristic of autoimmune diseases such as Raynaud's phenomenon (RP), arthralgias, myalgias, or a positive anti-nuclear antibody (ANA), but not meet criteria for a defined condition; in those cases, the diagnosis may not be obvious. Such patients are often diagnosed as "UCTD." Other patients may meet criteria for two or more defined autoimmune conditions; these patients are often referred to as having an "overlap syndrome." MCTD is one such overlap syndrome, and will be discussed further in this article.

## Undifferentiated Connective Tissue Disease

Patients who have symptoms and laboratory findings consistent with a systemic CTD, but do not meet the criteria for classification of a

particular disease are often considered to have UCTD. This concept was initially proposed by LeRoy and colleagues in 1980[1] to refer to the early phases of connective tissue diseases that were initially undefined; they questioned whether a portion of these patients might remain undifferentiated indefinitely or experience complete remission or whether they might all eventually develop a defined autoimmune disease. There are not defined criteria for such patients; however, these patients often have laboratory evidence of positive anti-nuclear antibodies without specific autoantibodies. RP as well as arthritis/arthralgias, nonspecific rash, or sicca symptoms are common features seen in these patients.

**Table 1**
Specific overlap syndromes and associated auto-antibodies.

| Auto-antibodies | Clinical Features |
|---|---|
| Anti U1-snRNP Ab (MCTD) | SLE+ myositis+ scleroderma+ RA |
| Anti PM-Scl Ab | Myositis + Raynaud's |
| Anti synthetase Ab (Jo-1 etc) | Myositis + arthritis + interstitial lung disease |
| Anti SSA/B + RF+ anti CCP Ab | RA + Sjogren's |

Studies have observed cohorts of patients diagnosed with UCTD for several years. Bodolay, et al reported on 665 Hungarian patients with UCTD followed for five years.[2] In that cohort, 34% of the patients eventually developed a well-defined CTD: RA in 13.1%, Sjogren's syndrome in 6.8%, SLE in 4.2%, scleroderma, in 2.8%, MCTD in 4.0%, systemic vasculitis in 3.3% and myositis in 0.5%. 12.3% of the patient's achieved complete remission. They observed that the highest probability of evolution to a differentiated CTD is within the first two years after onset of symptoms.

In another study, a U.S. multi-institutional outpatient inception cohort of 213 UCTD patients was evaluated after ten years.[3] The patients were divided into three categories: isolated RP (31 patients), unexplained polyarthritis (UPA) (67 patients), and UCTD (115 patients) defined as meeting at least three of 11 specific manifestations of connective tissue disease. In the 115 UCTD patients, 47 were lost to follow up. Twelve patients had died (one with RA and one with SLE). Twelve patients were in remission, six patients developed RA, eleven were diagnosed with SLE, three with systemic sclerosis, one with psoriatic arthritis, and one was diagnosed with myasthenia gravis. The remaining 26 continued to have unclassified disease.

Other groups have examined similar patients;[4-7] an average of 30% of UCTD eventually developed a defined CTD, while the majority remained active but with undifferentiated disease. Fortunately, in patients who remained undifferentiated, there tended to be absence of major organ involvement.

Since evolution to a defined CTD can occur, it is important to monitor these patients regularly, especially during the first two years of manifestations, or during conditions which may interfere with the course of an autoimmune disease such as severe infection or pregnancy. Careful management of UCTD patients is reasonable, but at times difficult. Consideration of the severity of the symptoms, potential for organ damage, and potential responses or side effects to treatment must be weighed. Often the symptoms can be managed with non-steroidal anti-inflammatory drugs (NSAIDs) and hydroxychloroquine for musculoskeletal symptoms or serositis, and calcium channel blockers for Raynaud's symptoms.

## Auto-Antibodies

Characteristics of autoimmune connective tissue diseases generally include the presence of autoantibodies combined with particular clinical characteristics. There is increasing evidence that the development of autoantibodies precedes the clinical manifestations of the disease in question; these autoantibodies are often involved in the disease pathogenesis.[8, 9] Researchers have reported numerous clinical correlations or particular patterns of clinical features associated with specific autoantibodies. The presence of a particular autoantibody may not only be frequently associated with a particular disease, but a particular manifestation of that disease. Presence of specific auto antibodies should often raise suspicion and vigilance for particular diseases or patterns of clinical involvement. A complete review of autoantibodies can be found in the article by Moore in this issue of Missouri Medicine on page 140.

## Overlap Syndromes

Overlap syndromes are generally defined as meeting criteria for more than one classic autoimmune CTD. Patients may present with evidence of more than one disease simultaneously or they may develop different diseases sequentially. Some patients may exhibit two or more diseases with characteristic serologic markers for those conditions. At times it can be useful to categorize patients based on patterns of clinical features. Over time researchers have studied groups of patients with similar overlap clinical

**Table 2**
Criteria for Classification for Mixed Connective Tissue Disease
Alarcon-Segovia and Villarreal

**Serologic**

- anti-RNP at a titer of ≥1:1,600

**Clinical Criteria**

- Myositis or synovitis + 2 of following
  - edema of the hands
  - synovitis
  - myositis
  - Raynaud's phenomenon
  - sclerodactyly/acrosclerosis

features and identified specific autoantibodies, which have helped further define some overlap syndromes and facilitate disease management.[10] Examples of these overlap syndromes and autoantibody associations can be seen in Table 1. A full discussion of these overlap syndromes is beyond the scope of this article; however, one particular overlap, MCTD, will be discussed further.

## Mixed Connective Tissue Disease

MCTD was initially described by Gordon C. Sharp, MD and William S. Irvin, MD during their training at Stanford University.[11] Subsequently, both practiced rheumatology in Columbia, Missouri. Dr. Sharp was Chairman of the Division of Immunology and Rheumatology at the University of Missouri for many years. Many of the early long term investigations and follow-up of the patients with MCTD were done at the University of Missouri under his leadership. (See Sidebar on page 66.)

MCTD was originally described as a connective tissue disorder characterized by the presence of high titers of a distinct autoantibody to ribonucleoprotein and clinical features of SLE, systemic sclerosis, and polymyositis. RA was later added to the mix. The autoantibody was later found to be anti-U1 RNP antibody. MCTD was the first overlap syndrome that was defined in terms of association with a specific autoantibody. Whether MCTD should be thought of as a distinct entity or merely a subcategory of a defined connective tissue disease has been a matter of debate; however over time the unique characteristics of these patients have been well delineated and have helped us to better understand a number of overlap syndromes.

## Clinical Features

Serologically, the first clue to a diagnosis of MCTD is a very high titer ANA and anti U1-RNP antibodies. Absence of other specific autoantibodies is also important. Antibodies to double-stranded DNA (dsDNA), Sm, and SSA/SSB are occasionally seen as transient phenomenon, but when they are found as the predominant antibody, the clinical course is typically more consistent with SLE.

Although MCTD is an overlap of SLE, scleroderma, myositis, and RA, the overlap of these conditions typically occurs sequentially over time rather than simultaneously. Early in the course of disease, patients may have somewhat nonspecific symptoms such as fatigue, myalgias, arthralgias, and Raynaud's phenomenon. Often, initially a diagnosis of UCTD is most appropriate given the full clinical picture. The most common clinical associations include hand edema, arthritis, RP, inflammatory muscle disease, and sclerodactyly. A high titer ANA and anti-U1 RNP should alert the clinician to follow the patient closely over time for the development of MCTD.[12]

Although there are no American College of Rheumatology criteria for the classification of MCTD, several criteria for classification have been published.[13] Many clinicians favor the criteria proposed by Alarcon-Segovia and Villarreal [14] based largely on simplicity and general applicability.[15] They are shown in Table 2. These criteria incorporate some of the early features seen in MCTD.

Over time many organ systems may be involved in MCTD.[16] Greater than 90% of patients experience arthralgias and 50-60% have arthritis. Rheumatoid factor and anti-CCP antibodies may be positive. As mentioned, myalgias are common and myositis may be seen in up to 70% of patients. There are typically mild muscle enzyme abnormalities. The myopathy typically responds well to corticosteroids and does not remain a prominent feature over time. Histologically the inflammatory myopathy is similar to idiopathic inflammatory myopathies with features of dermatomyositis and polymyositis.

Hematologic abnormalities are often seen in patients. They may have anemia, as well as leukopenia, lymphopenia, and thrombocytopenia. Dryness of the eyes and mouth is also seen. Esophageal dysmotility is common with occasional dysphasia. Pericarditis is the most common type of cardiac involvement. Profound central nervous system involvement is rare, but patients may experience headaches or trigeminal neuralgia. Peripheral nervous system involvement may be seen with polyneuropathy. Renal involvement is also relatively rare. Glomerulonephritis is typically membranous rather than proliferative. Scleroderma-like renal crisis has also been reported.

Dermatologic features may be varied. RP is an early feature in more than 90% of patients. Digital infarcts may be seen as well, in some patients. Sclerodactyly and nail fold vascular changes are also common. Truncal scleroderma is rare. Skin rashes may resemble lupus or dermatomyositis.

Pulmonary symptoms occur in up to 75% of patients. Patients may complain of cough, dyspnea on exertion, or pleuritic chest pain. Physical exam may be unremarkable or may demonstrate basilar rales. Interstitial lung disease may be seen in up to 50% of patients. Pulmonary hypertension is prognostically the most severe form of pulmonary involvement and is the most common disease related cause of death. Pulmonary arterial hypertension in MCTD is usually caused by bland intimal proliferation and medial hypertrophy of pulmonary arterioles, which is the characteristic vascular lesion in this disease. At times the presence of antiphospholipid antibodies in patients also correlates with the development of pulmonary hypertension. Decreased diffusing capacity of the lung for carbon monoxide (DLCO) is a sensitive measure for detecting pulmonary involvement. At times pulmonary involvement may help to distinguish patients with MCTD from those with lupus where pulmonary hypertension is less common.

## Management of MCTD

Management of MCTD is compounded by the absence of controlled trials. Recommendations are based on conventional treatments for the specific autoimmune diseases of SLE, myositis, RA and scleroderma. Therapy for specific manifestations is reasonable such as NSAIDs or antimalarial medications for arthralgia, or calcium channel blockers for RP. Recent advances in the treatment of pulmonary hypertension have led to reduced morbidity and mortality. Consideration of the effects of medication on all aspects of a patient's disease process is prudent in patients with MCTD or any overlap. For example, one should use caution with the use of methotrexate because of the concern for pulmonary toxicity or with the use of TNF inhibitors because of the concern for exacerbation of the SLE activity in a patient. Some symptoms may be responsive to short courses of corticosteroids; however, the long-term use of corticosteroids in these patients is not always appropriate and may lead to premature atherosclerosis or osteoporosis.

Monitoring for development of pulmonary disease is important with regular chest radiographs, annual pulmonary function studies including DLCO, and annual 2-D echocardiogram with Doppler for estimation of systolic pulmonary artery pressure to evaluate for pulmonary hypertension.

## Outcome/Prognosis

The initial description of MCTD indicated that the patients had a relatively favorable prognosis with no renal involvement identified. Over time, renal disease has been recognized in some patients, but severe renal disease is uncommon. The prognosis is not generally as favorable as initially perceived however, with pulmonary disease, particularly pulmonary hypertension, contributing to the worst prognosis.

A report of long-term outcome of patients followed at University of Missouri for up to 29 years observed a favorable outcome in 62% of the patients.[17] However, 38% had continued active disease or had died. 11 patients had died although two patients had been in a prolonged remission prior to their deaths. Most of the patients who died had pulmonary hypertension. In that study, the most frequent histopathological finding at autopsy was intimal proliferation and medial hypertrophy of arteries. In the lungs, the proliferative vascular lesions occurred with little or no interstitial fibrosis.

In another study from Hungary, 280 patients with MCTD were followed prospectively for up to 15 years.[18] Five, Ten, and 15 year survival rates after diagnosis were 98, 96%, and 88% percent respectively. A total of 22 patients' died. The cause of death was pulmonary arterial hypertension in nine, TTP in three, infection in three, and cardiovascular events in seven.

It is clear that the course of MCTD is varied, and many patients do follow a benign course. However, some patients have increased morbidity and mortality, and the most serious complication is the development of pulmonary hypertension. Identification of patients with or at risk for MCTD is important in order to institute appropriate monitoring and therapy when indicated.

## Conclusion

The complexity and relative infrequency of autoimmune diseases can contribute to confusion and misunderstanding for non-rheumatology health care providers and patients. When patients exhibit symptoms of more than one condition, the problem may be compounded. Recognition of the existence of overlap syndromes such as MCTD and knowledge of autoantibodies identifying risks for certain clinical manifestations is one step toward a better understanding of these conditions. Additionally recognizing that many patients do not fulfill criteria for a particular autoimmune disease; yet require

## Gordon C. Sharp, MD, did much of the seminal work in MCTD

The Antinuclear Antibody Laboratory at the University of Missouri School of Medicine was renamed the Gordon C. Sharp ANA Laboratory in a ceremony held on June 7, 2010. Dr. Sharp, Professor Emeritus of Immunology and Rheumatology, founded the ANA laboratory 32 years ago and has served as the laboratory director or co-director until September of 2009.

The ANA laboratory is recognized as one of the best in the nation, receives specimens from across the nation, and has become the repository for thousands of patient serum samples from around the country and beyond, providing a data base that offers research material for many of our faculty and fellows. The information reported by the ANA laboratory has enabled the early detection, definitive diagnosis, treatment, and exclusion of many potentially devastating autoimmune and rheumatic diseases. Dr. Sharp's vision and leadership has brought this laboratory to a high level of international recognition and esteem among peer institutions. Dr. Sharp has also ensured the laboratory's excellent reputation by continually updating its test panels as new scientific discoveries are made.




In the photo above, David A. Fleming, MD, Chair, MU Department of Medicine (left), Gordon C. Sharp, MD, MU Emeritus Professor of Immunology & Rheumatology.

monitoring for development of a specific disease process or additional features of autoimmunity is important. Prudent therapy to improve outcomes and quality of life for these patients is critical.

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## Disclosure

None reported.

MM

# A Retrospective Study on Infant Bed-sharing in a Clinical Practice Located in an Urban Cluster

*by Patricia J. Norton, MD & Kathrene D. Valentine, BS, MS*

**Implementing education before delivery gives the family the time and information needed in order to prepare a safe sleep environment before the baby's arrival home.**



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## Abstract

**Objectives: This retrospective study evaluates infant bed-sharing at a Missouri family practice with OB care.**

**Methods: After Institutional Review Board (IRB) approval, data were extracted from the first four well-child visits of 2374 infants between Sept. 2003 and Dec. 2011.**

**Results: Bed-sharing decreased after 2005 (25%, 39%, respectively, p = 0.000). For infants who bed-shared, the frequency of bed-sharing did not decline.**

**Conclusions: Nearly 20% of infants bed-share before the first visit; safe sleep prenatal education is warranted.**

## Introduction

Studies have confirmed bed-sharing as a known risk factor for sleep-related infant deaths.[1, 2] In 2005 the American Academy of Pediatrics' (AAP) Task Force on Sudden Infant Death Syndrome (SIDS) stated a new recommendation to reduce the incidence of sleep-related deaths: "infants not bed-share during sleep."[3] In 2011 AAP's Task Force on SIDS reiterated their previous recommendation against bed-sharing.[4] Additionally, the 2011 Task Force stated "a crib, bassinet, or portable crib/play yard that conforms to the safety standards of the Consumer Product Safety Commission and ASTM International...is recommended" for every sleep.[4] These recommendations were supported by many other institutions, most notably the U.S. Consumer Product Safety Commission[5, 6] and the National Institute of Child Health and Human Development (NICHD).[7, 8]

The 2011 Task Force also recommended "Continue research and surveillance on the risk factors, causes, and pathophysiological mechanisms of SIDS and other sleep-related infant deaths."[4]

Since the AAP's 2005 new recommendation against bed-sharing, we know of only four prevalence studies on bed-sharing in infants, six months of age or less, which included data after 2005: Hauck et al. study[9] (May 2005 to June 2007), Krouse et al. 2008 study[10] (A. Krouse, Phd, written communique, August 2013), the first author's previous study[11], Norton and Grellner (March 2002 to April 2008), and the ongoing National Infant Sleep Position Study[12] (NISP) 1993-2010.

In the Hauck study,[9] of approximately 2,300 infants nationwide, bed-sharing rates were as followed; 1 month of age, 42.5%; 3 months, 34.0%; and at 6 months, 30.7%. This study did not evaluate

whether a change in the rate of bed-sharing occurred with the new AAP's recommendations. The Krouse et al. study of 2008 was a limited study of 94 new mothers in Pennsylvania; 47% of mothers reported bed-sharing at one month of age and 17% at three months of age. [10]

Norton and Grellner (2010),[11] studying the infant population of a clinical practice in an urban area: 1 month of age, 18%; 3 months, 18%; and at 6 months, 14%. NISP (1993-2010) study found bed-sharing rates increasing for black and Hispanic infants throughout the study period. However among white infants rates of bed-sharing did not change.[12] In the Norton and Grellner (2010) study,[11] the bed-sharing rate decreased significantly after AAP's recommendation against bed-sharing in 2005.

The objectives of this study were fourfold:

1) to continue surveillance of the rate of bed-sharing;

2) to identify the prevalence of bed-sharing and other unsafe sleeping practices in an infant population of a rural/urban cluster;

3) to examine the independent variables associated with bed-sharing; and

4) compare this current study with the first author's previous study noted above.

The term "bed-sharing" referred to a parent(s) and/or other adults or children sleeping with an infant.[3]

## Methods

### *Study Population and Design*

This study utilized electronic medical records (EMR) from a private practice of family medicine with obstetrical care (OB) in Missouri. The practice was located in an urban cluster (populations between 2,500–49,999) and was surrounded by rural areas as determined by the U.S. Census[13,14] of 2000 and 2010. The nearest urban area was 40 miles away. After approval for the study from the participating medical institution's Institutional Review Board was received, a document query of the EMR from the institution was completed. We obtained the de-identified EMRs of all infants who had presented to the designated family practice office for any of their initial four well-child visits from September 2003-December 2011.

Infants were excluded from the study for three reasons:

1) no sleep location was recorded at any of the well-child visits;

2) their first well-child visit occurred prior to the beginning of use of EMRs in the office (Sept. 2003); or

3) their birth date (month and year) precluded completion of the fourth well-child visit before the end of study's time frame. Thus, infants born between September 2003 and April 2011 comprised the total cohort. Chart reviews were completed by hand of each well-child visit as marked in the EMR. Age at the visits was categorized as follows: newborn to one month (first well-child visit), two to three months (second well-child visit), four to five months (third well-child visit), and six to eight months (fourth well-child visit). None of the infants in the previous study were in the current study.

### *Measurement of Dependent and Independent Variables*

During routine well-child visits, data were recorded into the EMR by the health care professionals working in the family practice office. The office used the EMR system called "Centricity" (S. Fair, written communication, May 2013). The EMR contained a section labeled "Sleeping" which prompted health care professionals to inquire about the infant's sleep environment. For the first four well-child visits, a simple checklist with three options were provided: "crib," "bassinet," "w/parent(s)." Addition, space were provided to add notes on sleep environment. Multiple sleep environments could be indicated.

Demographic variables obtained from the EMR included number of well-child visits, gender, social-economic status (SES), birth weight, hospital and/or ER visits, NICU admission, home apnea monitor use, social environment, and nutrition (i.e. all variables evaluated in the first author's previously cited study). In addition three more variables were examined: bassinet use, infants noted as having a chronic illness, and mode of delivery. These demographic variables were selected for evaluation as they might influence the caregivers in sleep location for their infants. Bassinet usage was examined in relation to sleep location when bassinet use was discontinued.

Low SES was designated to infants whose families received Medicaid, MO HealthNet (Missouri's health care assistance program), or who had no health insurance. High SES was designated by families with private or military medical insurance. The EMR recorded only one insurance type for each infant. Low birth weight (LBW) was defined as a weight $<$ 2500 grams. An infant's social environment was designated as "poor" (PSE) if health care professionals noted parental drug use, domestic violence, and/or Department of Family Services (DFS) involvement. Health status issues were analyzed using five parameters:

1) medical intervention--a report of a visit to the Emergency Department and/or hospitalization;

2) NICU admission with use of a home apnea monitor;

3) NICU only (NICU admission without use of home apnea monitor);

4) home apnea monitor use without recorded NICU admission; and

5) chronic illness as identified by the clinician at the third and/or fourth well-child visits. Infant nutrition was dichotomized between ever breastfed and not ever breastfed. Mode of delivery was either vaginal delivery (with or without instrumentation) or C-section.

### *Statistical Analysis*

These demographics were analyzed using multiple Pearson's chi-squared tests. All analyses were evaluated using a significance cutoff of $p < .05$. Analyses were run through version 19 of SPSS statistical software package (SPSS, Inc., Chicago, Ill).

## Results

Between September 2003 and December 2011, a total of 2,374 infants presented for their well-child visits (See Table 1). Out of these, 853 infants were present at all four well-child visits at the identified medical center. Whereas, the remaining 1,521 infants did not attend one or more well-child visits at the designated office (707 infants attended the first well-child visit, 1,091 attended the second, 842 attended the third, and 723 attended the fourth visit). Sleep location was not recorded in 1.5% of 6,775 visits (n=99). In the study, 66% had low SES (n=1,423) with WIC participation at 76%.

Bed-sharing was reported at least once during the four well-child visits for 29% of the total cohort (n=687) (See Table 2). Most families reported only bed-shared at one visit. Bed-sharing was most common at the first and second well-child visits with a decline in overall bed-sharing at the third and fourth well-child visits (See Table 2). Eighteen percent of

**Table 1** Demographics

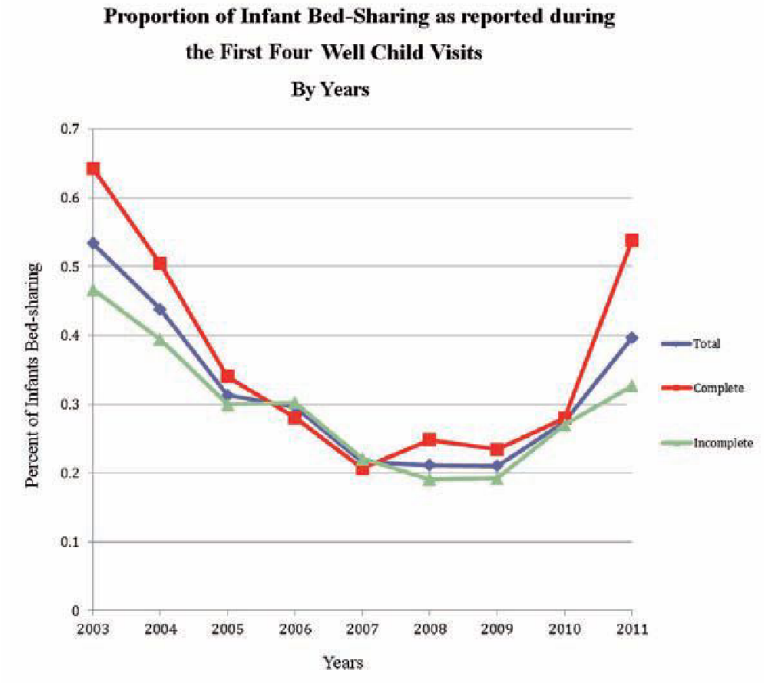
| | Total cohort | | Complete | | Incomplete | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Final cohort (number of infants) | 2374 | | 853 | | 1521 | |
| Complete: present at all 4 well-child visits | 853 | 35.9 | | | | |
| Incomplete: not present at all 4 well-child visits | 1521 | 64.1 | | | | |
| WIC[1] | 1598 | 76.2 | 611 | 76.6 | 987 | 75.9 |
| Male | 1246 | 52.5 | 437 | 51.2 | 809 | 53.2 |
| Low birth weight (LBW) < 2,500 g [2] | 90 | 6.5 | 47 | 6.4 | 43 | 6.6 |
| Went to ER or Hospital | 134 | 5.6 | 57 | 6.7 | 77 | 5.1 |
| NICU and apnea monitor | 15 | .7 | 10 | 1.2 | 5 | .3 |
| NICU only | 76 | 3.2 | 47 | 5.5 | 29 | 1.9 |
| Apnea monitor | 9 | .4 | 3 | .4 | 6 | .4 |
| PSE, domestic abuse, drug use, DFS | 32 | 1.6 | 6 | .7 | 26 | 1.7 |
| Chronic illness | 72 | 3.0 | 28 | 3.3 | 44 | 2.9 |
| Private or military insurance[3] | 751 | 34.5 | 286 | 36.4 | 465 | 33.5 |
| Public or no insurance[3] | 1423 | 65.5 | 500 | 63.6 | 923 | 66.5 |
| Nutrition (number of infants with data) | 2371 | | 853 | | 1518 | |
| Ever breastfed[4] | 1059 | 44.7 | 467 | 54.8 | 592 | 39.0 |
| Breastfed for ≤ 1 month | 340 | 14.3 | 147 | 17.2 | 193 | 12.7 |
| Breastfed for 2-3 months | 213 | 9.0 | 68 | 8.0 | 145 | 9.55 |
| Breastfed for 4-5 months | 149 | 6.3 | 54 | 6.3 | 95 | 6.3 |
| Breastfed for ≥ 6 month | 357 | 15.1 | 198 | 23.2 | 159 | 10.5 |
| Vaginal Delivery[5] | 840 | 64.0 | 456 | 64.7 | 384 | 63.3 |

[1]-No data were available on 276 infants
[2]- No data were available on 991 infants
[3]- No data were available on 200 infants
[4]- No data were available on 3 infants
[5]- No data were available on 1062 infants

**Table 2** Bed-sharing

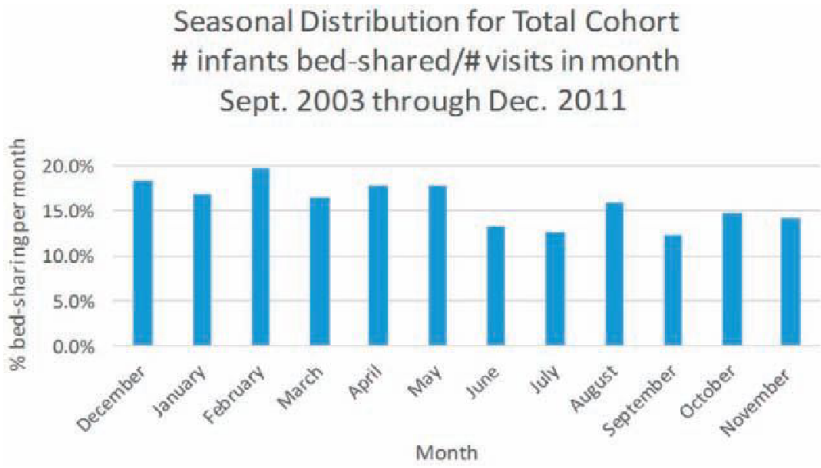
| | Total cohort | | Complete group | | Incomplete group | |
|---|---|---|---|---|---|---|
| | n = 2374 | % | n =853 | % | n = 1521 | % |
| Ever documented bed-sharing | 687 | 28.9 | 269 | 31.5 | 418 | 27.5 |
| Bed-shared once only | 422 | | 140 | 16.4 | 282 | 18.5 |
| Bed-shared twice only | 160 | | 63 | 7.4 | 97 | 6.4 |
| Bed-shared three times only | 82 | | 43 | 5.0 | 39 | 2.6 |
| Bed-shared all four times | 23 | | 23 | 2.7 | | |

Figure 1.



infants bed-shared before their first well-child visit.

Figure 1 shows the proportion of bed-sharing over the eight years of the study. It is important to note here that a full year of data was not collected on the first (2003) and last (2011) years on the graph. The rate of bed-sharing was analyzed from three perspectives. Infants born after 2005 (the year AAP first published its guidelines advising against bed-sharing) showed significantly less bed-sharing than those born in or before 2005 (25%, 39%, respectively, $p<0.000$). When looking at bed-sharing (yes/no) across years (a Spearman's Correlation), results are significant, negative, linear correlation for the total cohort ($r = -.125$, $p < .001$) which means that the trend is for less people, in general, to bed-share as the years progressed. However, in looking at bed-sharing (0, 1, 2, 3, 4 times) across years (again a Spearman's Correlation), which results in non-significant findings for the total cohort ($r = .002$, $p = .952$) meaning that no trend existed across years for all of these points.




Breastfeeding was reported by 45% of caregivers (n=1,059); 15% of the infants breastfed for at least 6 months (n=357). As shown in Table 3 infants who were ever breastfed were more likely to bed-share ($p<0.001$) at all four well-child visits ($p=0.005$, $p<0.001$, $p<0.001$, $p= 0.005$, respectively). Of the infants who completed all four well-child and breastfed for at least six months, they were more likely to bed-share at the third and fourth visits ($p=0.001$, $p<0.001$ respectively).

**Table 3** When bed-sharing occurred

| | Total cohort | | | Complete group | | | Incomplete group | | |
|---|---|---|---|---|---|---|---|---|---|
| | n = 2374 | # visits with data | % | n = 853 | # visits with data | % | n = 1521 | # visits with data | % |
| At 1st WC | 274 | 1531 | 17.9 | 143 | 839 | 17.0 | 131 | 692 | 18.9 |
| At 2nd WC | 345 | 1929 | 17.9 | 141 | 845 | 16.7 | 204 | 1084 | 18.8 |
| At 3rd WC | 241 | 1672 | 14.4 | 101 | 840 | 12.0 | 140 | 832 | 16.8 |
| At 4th WC | 220 | 1544 | 14.2 | 102 | 837 | 12.2 | 118 | 707 | 16.7 |

Those families with low SES were more likely to ever bed-sharing than families with high SES (26% vs 31%, $p= 0.008$). Upon analyzing each visit, this was significant at the third well child visit only ($p=.027$).

Interestingly, families reporting NICU admissions only were less likely to bed-share overall ($n=76$, $p = 0.005$). The LBW infants tended to show significantly less bed-sharing ($n=90$, $p = 0.001$). There was no significant difference in the rate of breastfeeding between LBW infants and non-LBW infants ($p= .9$).

When looking at the months that bed-sharing occurred, there were significant differences between months ($p = 0.007$). Figure 2 depicts the bed-sharing trend; bed-sharing was significantly higher in December through May than in June, July, September and November.

Although information was gathered on gender, WIC enrollment, bassinet usage, delivery method, hospitalization and/or ER visits, and chronic illness, none of these factors significantly altered bed-sharing in this sample (See Table 3). Because of a small sample sizes and/or small cell sizes, PSE, NICU patients who also used home apnea monitors, and those with just apnea monitors use could not be analyzed.

Alternative, non-approved sleep environments occurred in fewer than 2% of infants (n=58). Car seats and playpens were the most common alternative sleep environment (n=32) followed by swings (n=8). These fifty-eight infants were no more likely to bed-share at other well-child visits than infants sleeping in approved locations ($p = .559$).

Using chi-square tests, rates of infants in the complete group who "never" bed-shared in our study were compared with the rates available from Missouri Pregnancy Risk Assessment Monitoring System[15] (PRAMS) (2007: 79.2% vs 36.4%; 2009: 77.6% vs 42.5%; 2010: 75.0% vs 45.5%, respectively). Infants in our study were statistically significantly more likely to have "never" bed-shared compared with infants in the Missouri PRAM study. P-values were $<.001$ for each of the three years.

## Discussion

The results contains both encouraging and discouraging news. Because it only takes one episode of bed-sharing to

result in a fatality, it is significant that overall there has been a general trend toward more individuals never bed-sharing. However, for those who bed-share, the frequency of bed-sharing is not declining. We theorize that a trend of increased bed sharing may be occurring (See Figure 1). Data for 2010 and potentially 2011 (partial year of data collection) depict the influx of increased bed sharing. We speculate that this increase in recent years could be a result of many factors including:

1) caregivers' preference superseding safe sleep message;
2) lack of safe cribs;
3) ineffective guidance from health care community;
4) caregivers lack of awareness; or
5) potentially, the conflicting messages caregivers receive from various media.[16]

The rates of bed-sharing in our study different significantly from Missouri's PRAMS data. Previous studies have demonstrated different rates of bed-sharing based on race/ethnicity; bed-sharing rates are highest in black infants followed by Hispanic infants and least in white infants.[12,17] Race/ethnicity data for the study population were not available to us. In our study area the demographics[18] in 2010 were black, .3%; Hispanic, 7.0%; white, 91.5% while Missouri's demographics[19] in 2010 were black, 11.6%; Hispanic, 3.6%; white, 82.8%. The lower rate of bed-sharing in our study could reflect the lower breast feeding initiation rates compared with Missouri's PRAM study of rural women (54.8%, 66.1% respectively).[2°] However the women in our study were less likely to discontinue breast feeding prior to 2 months than the PRAM study of rural women (31.2 %, 43.8%, respectively).[20]

As in other studies, this study found bed-sharing is associated with infants ever having breastfed, [20, 21] breastfed for 6 months, and low social-economic status (SES). [21, 22, 23] In regard to independent variables associated with decreased bed-sharing (NICU only and LBW), the proportion of infants in both groups decreased after 2005.

In this study, seasonal distribution (December through May) was associated with higher bed-sharing than in June, July, September and November, whereas in the previous studies[11, 24] no association had been discovered. The seasonal distribution found in this study mirrors the seasonality noted historically in SIDS with highest rates in December to March with lowest rates in June to September.[25] This variable warrants further investigation.

Bassinet use and bed-sharing were examined to determine if bassinet user indicated the lack of crib availability and thus subsequent increase rate of bed-sharing. The 1,121 bassinet users (47% of the total cohort) were not associated with an increased or decreased risk of bed-sharing. (See Table 4.)

Recent studies have highlighted the need for NICU nurses to implement AAP's safe sleep practices in the NICUs and to educate parents on SIDS risk-reduction strategies.[26, 27] The decrease rate of bed-sharing of NICU infants in both studies is noteworthy. There was no significant difference in the rate of breastfeeding between NICU infants and non-NICU infants to explain the decrease rate of bed-sharing ($p = .990$).

An incidental finding was the perusal of the "Guidance" section of the EMR available to the healthcare professional.

**Table 4** Bassinet use

| | Total cohort | | Complete group | | Incomplete group | |
|---|---|---|---|---|---|---|
| | n = 2380 | % | n =853 | % | n = 1521 | % |
| Ever documented bed-sharing | 329 | 13.8 | 159 | 18.6 | 170 | 11.2 |
| Bed-shared once only | 203 | 8.5 | 85 | 10.0 | 118 | 7.8 |
| Bed-shared twice only | 85 | 3.6 | 45 | 5.3 | 40 | 2.6 |
| Bed-sheared three times only | 34 | 1.4 | 22 | 2.6 | 12 | 0.8 |
| Bed-shared all four times | 7 | 0.3 | 7 | 0.8 | | |

A healthcare provider could select from a list of over twenty potential topics that were discussed with a patient or write a topic in a comment section. "Co-sleeping" was a topic in the EMR list. In the NISP (1993-2010) study, caregivers that reported being advised by their physician against bed-sharing were less likely to bed-share.[12] EMRs designed to aid the physician in guidance on bed-sharing has the potential to decrease the incidence of bed-sharing.

One goal of this study was to replicate the previous study (a residency-based, family practice office with OB in an urban area) of Norton and Grellner (2010) for comparison to the current study (a private family practice with OB in an urban cluster). Overall, the current study replicated many of the previous findings. Both studies had similar reported rates of bed-sharing at least once during the four well-child visits (current study 29%; previous study 28%); a decrease in bed-sharing after 2005; the same three variables associated with bed-sharing: ever reported breastfeeding, breastfeeding for at least 6 months, and low SES. Similarly, NICU only infants and LBW infants had a decrease in reported incidence of bed-sharing. (See Table 5.)

## Limitations

All bed-sharing data relied on the knowledge and honesty of the caregiver accompanying the infant to the well-child visit. Sleep location data depended on the health care

**Table 5** Associations

| | Chi-square P-value | | | | |
|---|---|---|---|---|---|
| *Associations with increased bed sharing* | | | | | |
| Ever reported breast feeding | 0.000* | | | | |
| Breast fed at least 6 months (complete group) | 0.005* | | | | |
| Public or no health insurance (Low SES) | 0.008* | | | | |
| Bed-sharing as reported at each individual visit | | ≤ 1 month | 2-3 months | 4-5 months | 6-8 months |
| Incomplete cohort (infants with less than 4 WC visits) | | 0.338 | 0.225 | 0.005* | 0.012* |
| Ever reported breastfeeding | | 0.005* | 0.000* | 0.000* | 0.005* |
| Breastfed at least 6 months (complete group) | | 0.243 | 0.053 | 0.001* | 0.000* |
| Public or no health insurance (Low SES) | | 0.775 | 0.284 | 0.027* | 0.643 |
| *Associate with decreased bed-sharing* | | | | | |
| Before vs. After 2005 | 0.000* | | | | |
| NICU | 0.005* | | | | |
| Low birth weight | 0.001* | | | | |
| Seasonal distribution | 0.007* | | | | |
| Bed-sharing as reported at each individual visit | | ≤ 1 month | 2-3 months | 4-5 months | 6-8 months |
| Low birth weight | | 0.001* | 0.258 | ---- | ---- |
| *No association with bed-sharing* | | | | | |
| Gender | 0.272 | | | | |
| WIC | 0.137 | | | | |
| Method of delivery | 0.211 | | | | |
| Hospitalization or ER visit | 0.527 | | | | |
| Chronic Illness | 0.759 | | | | |
| Bassinet Use | 0.618 | | | | |

*Note.* The symbols "---" indicate a field that was unable to be analyzed due to small cell sizes.

* denotes statistical significance

professional follow through with the EMR prompts, both for obtaining the data and accuracy of recording.

Secondly, in the previous study not all well-child visits need have occurred at the designated family practice office in an urban area; some well-child visits could have come from any one of numerous clinics in the health care system. While in the current study all well-child visits occurred at the designated family practice office in an urban cluster.

Birth weight data were unavailable for 42% of the infants. Because birth weight was usually recorded at the first well-child visit and only occasionally at subsequent visits. LBW would be under reported in 55% of the infants who were not at the first well-child visit. Similarly, NICU admissions could be under reported in this group. Lack of data on ethnicity, maternal age, educational background, infant birth order, smoking, and alcohol use of household members, sleep position, and place of residence were other limitations to the study.

## Infant Bed-Sharing Recommendations

With nearly 20% of infants bed-sharing before the first well-child visit, providing patient education on safe beginning in the third trimester of pregnancy is warranted. If mothers are unprepared for a safe sleeping environment at the time of delivery, they will have difficulty arranging a safe sleep environment for the day of hospital discharge. Implementing education before delivery gives the family the time and information needed in order to prepare a safe sleep environment before the baby's arrival home. All residency programs for physicians providing obstetrical care need to include instruction to the residents on the most current safe sleeping practices of infants.

We recommend that EMR include a prompt for the medical care professional to counsel caregivers on safe sleeping practices including the risk of bed-sharing. Evaluation of EMR designs might highlight possible improvements to aid the physician with patient education in this area. We also recommend that software programs

be written for and used with EMR systems to facilitate data retrieval 1) for surveillance of risk factors associated with SIDS and other sleep-related infant deaths and 2) for evaluation of clinical and public health interventions aimed at reducing unsafe sleep environments.

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## Disclosure

None reported. **MM**


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